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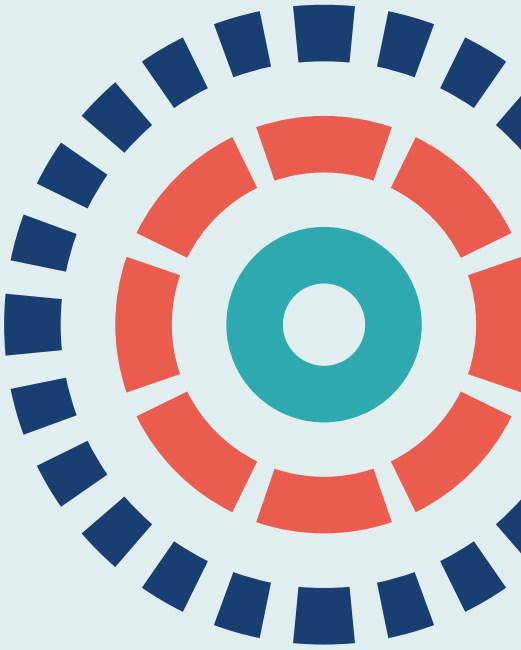

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This report

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Abstract

Lenvatinib and sorafenib for differentiated thyroid cancer after radioactive iodine: a systematic review and economic evaluation

Nigel Fleeman,[1]* Rachel Houten,[1] Adrian Bagust,[1] Marty Richardson,[1] Sophie Beale,[1] Angela Boland,[1] Yenal Dundar,[1] Janette Greenhalgh,[1] Juliet Hounsome,[1] Rui Duarte[1] and Aditya Shenoy[2]

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Background: Thyroid cancer is a rare cancer, accounting for only 1% of all malignancies in England and Wales. Differentiated thyroid cancer (DTC) accounts for ≈94% of all thyroid cancers. Patients with DTC often require treatment with radioactive iodine. Treatment for DTC that is refractory to radioactive iodine [radioactive iodine-refractory DTC (RR-DTC)] is often limited to best supportive care (BSC).

Objectives: We aimed to assess the clinical effectiveness and cost-effectiveness of lenvatinib (Lenvima®; Eisai Ltd, Hertfordshire, UK) and sorafenib (Nexar®; Bayer HealthCare, Leverkusen, Germany) for the treatment of patients with RR-DTC.

Data sources: EMBASE, MEDLINE, PubMed, The Cochrane Library and EconLit were searched (date range 1999 to 10 January 2017; searched on 10 January 2017). The bibliographies of retrieved citations were also examined.

Review methods: We searched for randomised controlled trials (RCTs), systematic reviews, prospective observational studies and economic evaluations of lenvatinib or sorafenib. In the absence of relevant economic evaluations, we constructed a de novo economic model to compare the cost-effectiveness of lenvatinib and sorafenib with that of BSC.

Results: Two RCTs were identified: SELECT (Study of [E7080] LEnvatinib in 131I-refractory differentiated Cancer of the Thyroid) and DECISION (StuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine-refractory thyrOid caNcer). Lenvatinib and sorafenib were both reported to improve median progression-free survival (PFS) compared with placebo: 18.3 months (lenvatinib) vs. 3.6 months (placebo) and 10.8 months (sorafenib) vs. 5.8 months (placebo). Patient crossover was high (≥ 75%) in both trials, confounding estimates of overall survival (OS). Using OS data adjusted for crossover, trial authors reported a statistically significant improvement in OS for patients treated with lenvatinib compared with those given placebo (SELECT) but not for patients treated with sorafenib compared with those given placebo (DECISION). Both lenvatinib and sorafenib increased the incidence of adverse events (AEs), and dose reductions were required (for > 60% of patients). The results from nine prospective observational studies and 13 systematic reviews of lenvatinib or sorafenib were broadly comparable to those from the RCTs. Health-related quality-of-life (HRQoL) data were collected only in DECISION. We considered the feasibility of comparing lenvatinib with sorafenib via an indirect comparison but concluded that this would not be appropriate because of differences in trial and participant characteristics, risk profiles of the participants in the placebo arms and because the proportional hazard assumption was violated for five of the six survival outcomes available from the trials. In the base-case economic analysis, using list prices only,

the cost-effectiveness comparison of lenvatinib versus BSC yields an incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained of £65,872, and the comparison of sorafenib versus BSC yields an ICER of £85,644 per QALY gained. The deterministic sensitivity analyses show that none of the variations lowered the base-case ICERs to < £50,000 per QALY gained.

Limitations: We consider that it is not possible to compare the clinical effectiveness or cost-effectiveness of lenvatinib and sorafenib.

Conclusions: Compared with placebo/BSC, treatment with lenvatinib or sorafenib results in an improvement in PFS, objective tumour response rate and possibly OS, but dose modifications were required to treat AEs. Both treatments exhibit estimated ICERs of > £50,000 per QALY gained. Further research should include examination of the effects of lenvatinib, sorafenib and BSC (including HRQoL) for both symptomatic and asymptomatic patients, and the positioning of treatments in the treatment pathway.

Study registration: This study is registered as PROSPERO CRD42017055516.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

AE	adverse event
AG	Assessment Group
ANOVA	analysis of variance
AUC	area under the curve
BNF	*British National Formulary*
BSC	best supportive care
BTA	British Thyroid Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computerised tomography
DECISION	StuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine-refractory thyrOid caNcer
DTC	differentiated thyroid cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	US Food and Drug Administration
FDG	fludeoxyglucose
FTC	follicular carcinoma
HCC	hepatocellular carcinoma
H–H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPE	iterative parameter estimation
ITC	indirect treatment comparison
ITT	intention to treat
K–M	Kaplan–Meier
MAIC	matching-adjusted indirect comparison
MKI	multikinase inhibitor
MRI	magnetic resonance imaging
MTA	multiple technology appraisal
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
ORR	objective tumour response rate
OS	overall survival
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazard
PPS	postprogression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	performance status
PSA	probabilistic sensitivity analysis
PTC	papillary carcinoma
QALY	quality-adjusted life-year
RCC	renal cell carcinoma
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFTM	rank-preserving structural failure time model

RR	relative risk
RR-DTC	radioactive iodine-refractory differentiated thyroid cancer
SAE	serious adverse event
SELECT	Study of [E7080] LEnvatinib in 131I-refractory differentiated Cancer of the Thyroid
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
T_3	triiodothyronine
T_4	thyroxine
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

Plain English summary

What was the problem?

Differentiated thyroid cancer is a common type of thyroid cancer. For many patients, radioactive iodine is an effective treatment; however, for some patients, the treatment stops working or becomes unsafe. Two new drugs, lenvatinib (Lenvima®; Eisai Ltd, Hertfordshire, UK) and sorafenib (Nexar®; Bayer HealthCare, Leverkusen, Germany), may be new treatment options.

What did we do?

We reviewed the clinical evidence of lenvatinib and sorafenib. We also estimated the costs and benefits of treatment.

What did we find?

Compared with no treatment, treatment with lenvatinib or sorafenib may increase the time that people live with thyroid cancer before their disease gets worse; however, both drugs are expensive and may have unpleasant side effects.

What does this mean?

At their published (undiscounted) prices, lenvatinib or sorafenib may not be considered to provide good value for money to the NHS.

Scientific summary

Background

Thyroid cancer is a rare cancer, accounting for only 1% of malignancies in England and Wales. Differentiated thyroid cancer (DTC) accounts for approximately 94% of thyroid cancers. For patients with DTC, the overall 10-year survival rate for middle-aged adults is 80–90%.

Treatment of DTC usually involves surgery. Following surgery, it is generally recommended that patients undergo treatment with radioactive iodine. Treatment for DTC refractory to radioactive iodine [radioactive iodine-refractory DTC (RR-DTC)] is often limited to best supportive care (BSC).

Two oral anti-cancer treatments for RR-DTC, used within their licensed indications, are the focus of this review: lenvatinib (Lenvima®; Eisai Ltd, Hertfordshire, UK) and sorafenib (Nexar®; Bayer HealthCare, Leverkusen, Germany). Both are types of tyrosine kinase inhibitors (TKIs) known as multikinase inhibitors.

Clinical advice to the Assessment Group (AG) is that in clinical practice there are concerns about the toxicity of TKI therapy in patients and consequent effects on the quality of life of patients with asymptomatic disease. This means that treatment tends to be given only to patients who are symptomatic or only when clinically significant progressive disease develops.

Objectives

The remit of this research was to assess the clinical effectiveness and cost-effectiveness of lenvatinib and sorafenib within their European Union marketing authorisations for the treatment of patients with RR-DTC.

Review methods

The research involved systematic reviews of clinical and cost-effectiveness evidence, including evidence provided by the companies that manufacture lenvatinib (Eisai Ltd) and sorafenib (Bayer HealthCare). The AG also carried out its own evidence review and developed a de novo economic model.

Five electronic databases were searched (on 10 January 2017) for randomised controlled trials (RCTs), systematic reviews, prospective observational studies and economic evaluations. References in the systematic reviews identified during the AG's review and the professional stakeholder submissions, received as part of the National Institute for Health and Care Excellence (NICE)'s multiple technology appraisal process, were cross-checked to identify any relevant studies that the AG's search may have missed. Only studies of lenvatinib or sorafenib for treating RR-DTC were included. Clinical effectiveness outcomes included overall survival (OS), progression-free survival (PFS), objective tumour response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL). Cost-effectiveness outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts, applied inclusion criteria to relevant publications, and quality assessed the included studies. The results of the data extraction and quality assessment were summarised in structured tables and by narrative description. The AG constructed a de novo economic model comparing the cost-effectiveness of lenvatinib and sorafenib with BSC.

Results from the systematic reviews

Evidence from randomised controlled trials

Two relevant Phase III, multicentre, double-blind RCTs were identified: SELECT (Study of [E7080] LEnvatinib in 131I-refractory differentiated Cancer of the Thyroid) (lenvatinib vs. placebo) and DECISION (StuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine-refractory thyrOid caNcer) (sorafenib vs. placebo).

The proportions of patients in these trials who were asymptomatic at baseline are unknown; however, the European Public Assessment Report for sorafenib reports that 20% of patients in DECISION were retrospectively considered to be symptomatic.

The AG considered both trials to be well conducted and of good quality; however, there were some differences in trial and patient characteristics, both within and across the two trials. Owing to event hazards being proportional over time only for DECISION-unadjusted OS, all other hazard ratio results from SELECT and DECISION should be interpreted with caution.

The primary outcome in both trials was PFS, assessed by blinded independent review, using data from the first data cut-off point (after a median of 17 months' follow-up in both trials). Results from SELECT show that treatment with lenvatinib improved median PFS compared with placebo (18.3 vs. 3.6 months, respectively). Results from DECISION show that treatment with sorafenib improved median PFS compared with placebo (10.8 vs. 5.8 months, respectively). Results from the post hoc subgroup analyses of data collected from symptomatic and asymptomatic participants show that median PFS for asymptomatic and symptomatic participants treated with sorafenib is similar (10.8 vs. 10.7 months, respectively); however, for participants treated with placebo, the median PFS of asymptomatic participants is twice that of symptomatic participants (7.2 vs. 3.6 months, respectively).

The OS results from SELECT and DECISION at the third data cut-off point (after approximately 38 and 36 months' follow-up, respectively) showed no statistically significant differences between trial arms; however, patient crossover was high ($\geq$ 75%) in both trials, confounding OS estimates. When OS results from both trials were adjusted for treatment crossover, the only statistical difference between arms was in SELECT, favouring lenvatinib over placebo.

The ORR in both trials was reported based on data from the first data cut-off point. ORR in SELECT was 64.8% in the lenvatinib arm and 1.5% in the placebo arm. ORR results for the sorafenib and placebo arms of DECISION were 12.2% and 0.5%, respectively.

Analyses of safety data from SELECT and DECISION were reported from the first data cut-off point. Results show that treatment with both lenvatinib and sorafenib led to an increase in the incidence of AEs versus treatment with placebo (in particular, hypertension and hand–foot syndrome, respectively). The median time to onset of AEs suggests that most AEs typically occur early, with a decrease in incidence, prevalence and severity over time. Dose reductions were frequent (> 60%) in both trials.

Health-related quality-of-life data were collected only as part of DECISION. At baseline, HRQoL scores were considered to be comparable to a normative adult cancer population; however, at the first assessment (cycle 2, day 1), HRQoL scores worsened in the sorafenib arm whereas the scores for the placebo arm remained very similar to the baseline score. Thereafter, the sorafenib arm scores remained similar to the scores at first assessment, whereas the placebo arm scores remained similar to the baseline scores.

Prespecified subgroup analyses were conducted for OS, PFS and ORR in SELECT and for PFS in DECISION. All findings favoured the intervention (lenvatinib or sorafenib) when compared with placebo.

Both trials also included extended open-label phases including patients who had crossed over from placebo to lenvatinib or sorafenib on disease progression. The extended open-label phase of DECISION also involved patients who received additional sorafenib on disease progression. The efficacy findings for PFS from the extended phase of SELECT and DECISION were similar to the findings reported in the randomised phase of the trials. The incidence of AEs for patients treated with lenvatinib and sorafenib in the open-label phases of the two trials tended to be slightly lower than the incidence of those reported during the double-blind phase.

Indirect comparison

In the absence of direct clinical evidence comparing treatment with lenvatinib with treatment with sorafenib, the AG considered whether or not it would be appropriate to undertake an indirect treatment comparison. As SELECT and DECISION shared a common comparator (placebo), it is possible to construct a network; however, differences in participant characteristics, both within and between the trials, raised concerns about whether or not this approach was appropriate. The AG examined the PFS Kaplan–Meier data and concluded that the risk profiles of the populations in the two placebo arms were not comparable. In view of these issues, the AG concluded that it was not appropriate to undertake an indirect comparison, and considered that the results generated by any indirect comparison that included data from SELECT and DECISION should be interpreted with caution. Therefore, the AG could not conclude whether the effectiveness of treatment with lenvatinib and effectiveness of treatment with sorafenib are similar or different.

Evidence from other reviews and prospective observational studies

Thirteen studies were included in the AG's review of systematic review evidence, including those reviews conducted by Eisai Ltd and Bayer HealthCare, provided within their company submissions. Nine studies were included in the AG's review of prospective observational studies. Unadjusted median OS estimates for patients treated with lenvatinib and sorafenib in SELECT and DECISION tended to be higher than those reported in the reviewed prospective observational studies, whereas median PFS and ORR estimates tended to be lower. Results from indirect comparisons conducted by the authors of systematic reviews showed PFS (but not OS) to be statistically significantly improved with lenvatinib, when compared with sorafenib. Overall, the safety findings from the RCTs were consistent with the findings from the prospective observational studies and systematic reviews of lenvatinib and sorafenib. Results from indirect comparisons conducted by the authors of two systematic reviews showed lenvatinib to result in statistically significantly fewer cases of alopecia but statistically significantly more cases of hypertension, serious adverse events, treatment-related serious adverse events and withdrawals owing to AEs, when compared with sorafenib.

Evidence from cost-effectiveness studies

The two submitting companies and the AG agreed that there are no published cost-effectiveness studies relevant to the decision problem set out in the final scope issued by NICE.

Company submissions (economics)

Both companies submitted economic evidence generated by de novo economic models. Using list prices, the Eisai Ltd base-case incremental cost-effectiveness ratio (ICER) for the comparison of treatment with lenvatinib and treatment with sorafenib is £22,491 per QALY gained; for the comparison of treatment with lenvatinib and BSC, it is £48,569 per QALY gained. The analyses carried out by Bayer HealthCare used the Commercial Medicines Unit price for sorafenib and the list price for lenvatinib. The Bayer HealthCare ICERs per QALY gained for the comparison of treatment with sorafenib and treatment with lenvatinib, and treatment with sorafenib and BSC, are commercial in confidence and cannot be reported. Using the list price for sorafenib, the AG found that Bayer HealthCare's model generates an ICER per QALY gained of £56,417 for the comparison of treatment with sorafenib versus BSC.

Summary of the Assessment Group's cost-effectiveness results

The AG considered that it was inappropriate to compare data from SELECT and DECISION in the same evidence network, and concluded that it was not possible to carry out a cost-effectiveness analysis of lenvatinib versus sorafenib for patients with RR-DTC. Instead, the AG used a standard partitioned survival model structure, applied to the patient population specified in the final scope issued by NICE, to consider the cost-effectiveness of lenvatinib and sorafenib separately in comparison with BSC (as represented by the placebo arms of SELECT and DECISION, respectively). The design of the AG's model allowed each intervention to be represented in its natural time metric: 30-day cycles for lenvatinib and 28-day cycles for sorafenib. This involved creating two parallel models using the same assumptions and model parameters, but each with its own placebo arm calibrated from its respective clinical trial data.

The AG's base-case analysis, using list prices only, for the comparison of the cost-effectiveness of treatment with lenvatinib and BSC yields an ICER per QALY gained of £65,872, and for the comparison of sorafenib and BSC it yields an ICER per QALY gained of £85,644. The AG's deterministic sensitivity analysis involved varying 18 parameters, and the results of these analyses show that none of the variations lowers the AG's base-case ICERs below £50,000 per QALY gained. The AG's probabilistic sensitivity analysis results show that, compared with BSC, the probability of sorafenib being cost-effective at a threshold of £50,000 per QALY gained is $< 0.05\%$, and the probability of lenvatinib being cost-effective is 5.4%.

When the AG compared the cost-effectiveness of lenvatinib and BSC using placebo data from DECISION, and the cost-effectiveness of sorafenib and BSC using placebo data from SELECT, the ICERs per QALY gained approximately doubled (to £130,592) and halved (to £41,716), respectively. These results highlight that the choice of BSC comparator is very influential in this appraisal.

Discussion

Strengths

A key strength of this review is that it has brought together all the available relevant evidence (RCTs, observational studies, systematic reviews, indirect comparisons and cost-effectiveness studies) for assessing the clinical effectiveness and cost-effectiveness of treatment with lenvatinib versus sorafenib in patients with RR-DTC. The AG considered that SELECT and DECISION are good-quality, well-conducted trials.

Weaknesses and areas of uncertainty

Owing to a lack of confidence in any results generated by an indirect comparison, the AG considered that it is not possible to compare the relative effectiveness of treatment with lenvatinib with the relative effectiveness of treatment with sorafenib.

The generalisability of the findings of SELECT and DECISION to NHS clinical practice is questionable, as, in clinical practice, concerns about the toxicity of TKI therapy in patients, and consequent effects on the quality of life of patients with asymptomatic disease, means that treatment is generally only given to patients who are symptomatic or when clinically significant progressive disease develops. However, results from a post hoc analysis of DECISION data showed no difference in median PFS between symptomatic and asymptomatic patients (retrospectively categorised) treated with sorafenib.

Owing to a lack of HRQoL studies, there is considerable uncertainty around the HRQoL of patients with RR-DTC in general.

Conclusions

Compared with placebo, treatment with lenvatinib and sorafenib results in an improvement in PFS, ORR and possibly OS; however, compared with placebo, treatment with both drugs increases the incidence of AEs. Dose reductions with both drugs are, therefore, frequently required.

The AG considered that it is not possible to compare the clinical effectiveness or cost-effectiveness of lenvatinib with the clinical effectiveness or cost-effectiveness of sorafenib. This is primarily because the risk profiles of the participants in the placebo arms of SELECT and DECISION do not appear to be comparable.

Using list prices, compared with BSC, both treatments exhibit estimated ICERs of > £50,000 per QALY gained. Compared with BSC, the probability of sorafenib and lenvatinib being cost-effective at a threshold of £50,000 per QALY gained is < 0.05% and 5.4%, respectively.

Recommendations for research

These recommendations are ranked in order of priority.

1. Future clinical effectiveness research should focus on a head-to-head RCT that includes lenvatinib, sorafenib and BSC, and addresses the following questions:

    i. Should both symptomatic and asymptomatic patients be treated with lenvatinib and/or sorafenib?
    ii. How does treatment with lenvatinib and sorafenib affect the HRQoL of patients (progressed and non-progressed, and symptomatic and asymptomatic)?
    iii. What is the clinical effectiveness of lenvatinib and sorafenib compared with BSC and compared with each other?
    iv. How should lenvatinib, sorafenib and BSC be positioned in the treatment pathway?

2. The AG considered that it is important to explore more than just standard differences in participant and trial characteristics when considering the heterogeneity of studies that may be included in an indirect comparison. The AG suggests that, before undertaking an indirect comparison, the risk profiles of patient populations for the relevant outcome should be checked to confirm that they are proportional both within and across all trials that are being considered for inclusion in the network. This assessment would avoid generating indirect comparison results that are of unknown reliability.

Study registration

This study is registered as PROSPERO CRD42017055516.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Thyroid cancer: overview

Thyroid cancer is a rare cancer, representing only 1% of all malignancies in England and Wales.[1] It is caused by the growth of abnormal cells in the thyroid gland. This is a small gland at the base of the neck that secretes three hormones: triiodothyronine (T_3), thyroxine (T_4) and calcitonin. T_3 and T_4 control the rate of metabolism in the body, and calcitonin works with the parathyroid hormone to control the amount of calcium in the blood.[2] Thyroid cancer is usually asymptomatic and is often discovered incidentally via imaging studies [e.g. sonograms, computerised tomography (CT) scans and magnetic resonance imaging (MRI)] that are carried out for another reason, or when patients present with a large palpable nodule in the neck.[3] The actual diagnosis of thyroid cancer is usually made using ultrasonography and biopsy (typically, a fine-needle aspiration).[4]

The incidence of thyroid cancer is increasing worldwide.[4–10] In the UK, between the period 2003–5 and the period 2012–14, thyroid cancer incidence rates increased by 74% (*Figure 1*).[1] In 2014, there were 3404 patients diagnosed with thyroid cancer in the UK, 2941 in England and 123 in Wales.[1] The reasons for the increase in incidence are unknown, but are thought to be, at least in part, attributable to improved diagnostic and detection techniques.[11]

The incidence of thyroid cancer is 2.5 times greater in women than in men.[1] The reasons for this disparity are unclear.[12] Thyroid cancer incidence is strongly related to age, with the highest incidence rates being in older males, and the highest incidence rates among females being in younger and middle-aged women (*Figure 2*).

In the UK, thyroid cancer accounts for < 1% of male cancer deaths and < 1% of female cancer deaths.[13] The mortality rate in the UK is reported to be < 1 death per 100,000 people.[13] In 2014, there were 376 thyroid cancer deaths in the UK, 154 (41%) in males and 222 (59%) in females, giving a male-to-female ratio of around 7:10. In England and Wales, there were 331 thyroid cancer deaths: 137 in males and 194 in females.[13]

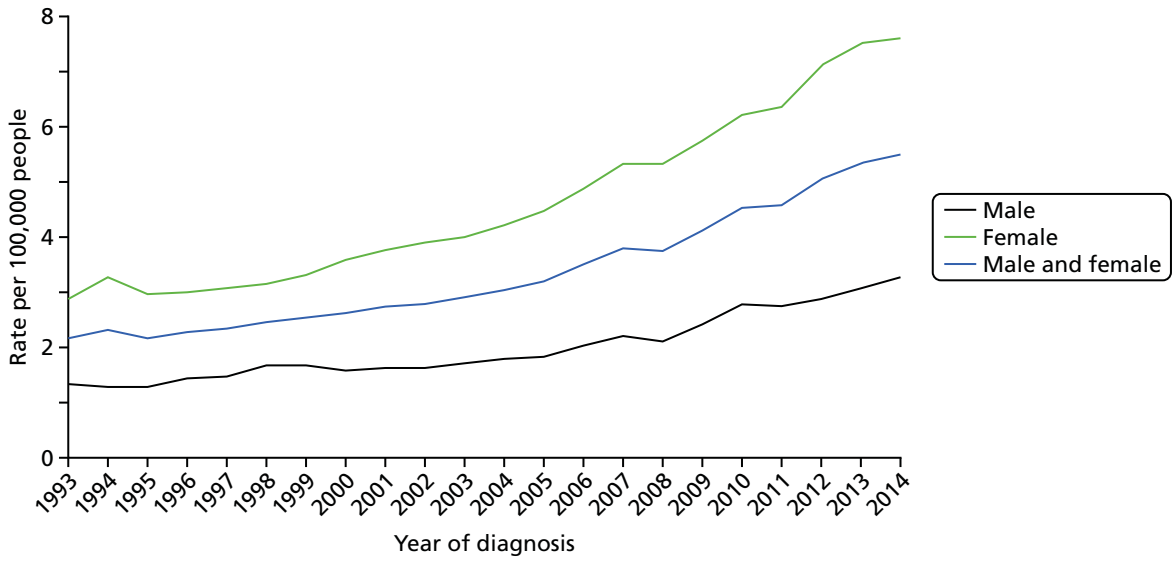

FIGURE 1 Average number of new cases per year per 100,000 people in the UK. Based on a graphic created by Cancer Research UK.[1]

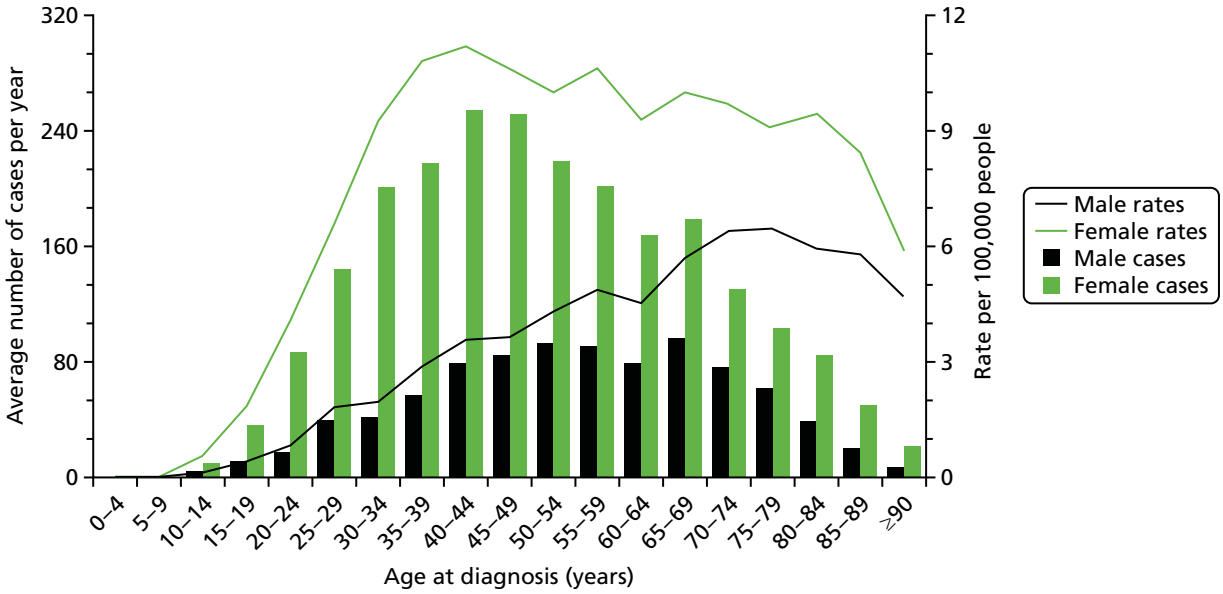

FIGURE 2 Age-specific incidence rates per 100,000 people in the UK. Based on a graphic created by Cancer Research UK.[1]

Although the incidence of thyroid cancer in the UK increased between the period 2003–5 and the period 2012–14, overall mortality rates remained stable during this time (*Figure 3*);[13] however, between 1970 and 2014, thyroid cancer mortality rates decreased by 46% in the UK, the decrease being more marked in females (54%) than in males (24%).[13] Mortality rates for thyroid cancer are projected to rise in the future: in the UK, it is expected that between 2014 and 2035 mortality will increase by 7%; however, the overall rate is expected to remain relatively low at 1 death per 100,000 people.[13]

Differentiated thyroid cancer

The most common form of thyroid cancer is differentiated thyroid cancer (DTC); DTC is reported to account for approximately 94% of thyroid carcinomas.[14,15] Less common types of thyroid cancer include medullary carcinoma and anaplastic carcinoma; these have been reported to account for approximately 4% and approximately 2% of all thyroid carcinomas, respectively.[15]

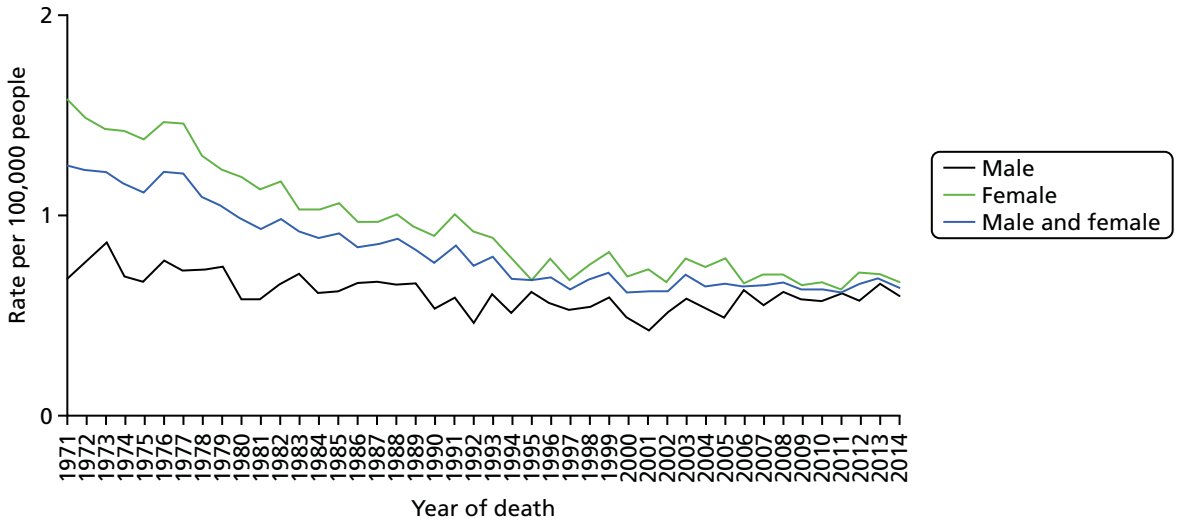

FIGURE 3 European age-standardised thyroid cancer mortality rates in the UK: 1971–2014. Based on a graphic created by Cancer Research UK.[13]

Differentiated thyroid cancer is a specific type of thyroid cancer made up of different subtypes including papillary carcinoma (PTC), follicular carcinoma (FTC) and Hürthle cell carcinoma. PTC is the most common type of DTC, accounting for approximately 83%[15] to 86%[16] of all cases; FTC accounts for approximately 10%[16] to 13%,[15] and Hürthle cell carcinoma accounts for approximately 3%[15] to 4%.[16] Hürthle cell carcinomas are usually grouped with FTCs because they present and behave similarly.[17]

The median age for all patients with DTC is reported to be 45 years;[18] however, estimates of the median age at onset for the subtypes of DTC have been reported to vary:

- Papillary carcinoma often affects people aged < 40 years,[17] but it is also reported that the median age of patients with PTC is 45 years.[19]
- The peak age for the onset of FTC has been stated to be between 40 and 60 years,[20] but, again, the median age has been reported to be approximately 45 years.[21]
- The median age of patients with Hürthle cell carcinoma has been reported to be 55 years.[21]

In general, the prognosis for patients with DTC is relatively good. The overall 10-year survival rate for middle-aged adults is reported to be 80–90%.[4] It has also been reported that > 85% of patients with DTC have a 'normal' life expectancy;[22] however, the prognosis generally gets worse with increasing age at the time of diagnosis, particularly for patients aged ≥ 45 years.[4] In addition, young children (aged < 10 years) are at higher risk of recurrence than older children.[4] Prognosis may also be affected by DTC subtype (histology). An analysis of US National Cancer Database data on 41,375 patients with DTC who were treated between 1985 and 1995[15] has shown that the 10-year relative survival for patients with PTC is 93%, whereas for patients with FTC it is 85%, and for patients with Hürthle cell carcinoma it is 76%.

The size and spread of the tumour affect prognosis. Studies cited by the British Thyroid Association (BTA)[4] are reported to show that the risk of recurrence and mortality correlates with the size of the primary tumour. Extrathyroidal invasion, lymph node metastases and distant metastases are also reported to be important prognostic factors.[4]

First-line treatment options for patients with differentiated thyroid cancer

There are currently no National Institute for Health and Care Excellence (NICE) guidelines and no NICE guidance for treating patients with DTC or any other type of thyroid cancer. Other clinical guidelines do present some recommendations. In chronological order from date of publication, relevant clinical guidelines include the European Society for Medical Oncology (ESMO) guidelines (2012),[23] BTA guidelines (2014),[4] American Thyroid Association guidelines (2015)[24] and National Comprehensive Cancer Network (NCCN) guidelines (2017).[25]

Owing to the indolent course of the disease, many patients with DTC, even if they have metastatic disease, do not require therapy for several years after diagnosis.[26] Treatments for DTC depend on factors including age, extent of disease, and histology, but usually involve surgery to remove all or part of the thyroid gland (thyroidectomy) followed by lifelong thyroxine for thyroid-stimulating hormone (TSH) suppression from the low–normal to fully suppressed range dependent on risk factors.[4,23–25]

Treatment options for patients with differentiated thyroid cancer that has progressed following surgery

Following initial surgery, it is estimated that between 5% and 20% of patients with DTC develop local or regional recurrences (approximately two-thirds of these involve cervical lymph nodes[27]) and between 10% and 15% of patients with DTC develop distant metastases.[4,24] The most common sites for metastases are

reported to be the lungs (50%), bones (25%), lungs and bones (20%) or other (5%).[24] It has been noted that the presence of bone metastases has been associated with a worse prognosis than metastases in other sites.[23]

The sites that DTC is most likely to spread to vary by histology. For patients aged > 40 years, it has been reported that 10% of patients with PTC, 25% of patients with FTC and 35% of patients with Hürthle cell carcinoma develop distant metastases.[28,29] PTC tends to spread to lymph nodes in the neck, whereas FTC usually spreads to the bones or lungs.[17] Hürthle cell carcinoma is more likely than FTC to spread to lymph nodes in the neck.[30]

A radioactive iodine uptake test is commonly used to determine whether or not DTC has spread. The test involves a patient being given a liquid or capsule containing radioactive iodine (iodine-123) to swallow. Two separate uptake measurements are then commonly obtained at different time points within a 24-hour period. The patient is then scanned to see how much of this radioactive iodine has been absorbed by the thyroid (radioactive uptake). Positive results (evidence of iodine-123 uptake) denote the presence of disease, whereas negative results (no radioactive uptake) denote the absence of disease.

It is recommended in clinical guidelines[4,23–25] that patients with DTC and evidence of radioactive iodine uptake should undergo treatment with radioactive iodine (also known as radioactive iodine ablation) to treat residual, recurrent or metastatic disease. Patients are typically tested 1–2 months after surgery. Radioactive iodine treatment has been used for > 60 years. It is administered in hospital (during an inpatient stay) and can be given to patients on more than one occasion, as necessary.[4]

Like the radioactive iodine uptake test used to diagnose DTC, radioactive iodine treatment involves swallowing radioactive iodine in either liquid or capsule form; however, the radioactive iodine is a different form (iodine-131) to that used for scans (iodine-123): the purpose of radioactive iodine treatment is to destroy cancerous cells. Thus, patients with iodine-131 uptake are responsive to treatment, which can be confirmed by imaging studies.

Approximately 33% of patients with advanced disease can be cured and many others achieve long-term disease stabilisation.[31] From published French registry data,[32] the 10-year survival rate for patients with distant metastases who successfully responded to treatment with radioactive iodine is 92%.[32]

Radioactive iodine-refractory differentiated thyroid cancer

Although for many patients radioactive iodine is an effective treatment, some patients become resistant to the treatment (decreased or no radioactive iodine uptake) or are unable to safely tolerate additional doses. These patients are considered to have radioactive iodine-refractory DTC (RR-DTC) and are the focus of this multiple technology appraisal (MTA).

Although clinical criteria and algorithms have been developed and reported in clinical guidelines,[4,23–25] there is no agreed precise definition of RR-DTC;[33] however, a review of the literature published in February 2017[31] highlights key features that can be considered in defining RR-DTC:

- Metastatic disease that does not take up radioactive iodine at the time of the first radioactive iodine treatment.
- Ability to take up radioactive iodine has been lost after previous evidence of uptake of radioactive iodine.
- Radioactive iodine uptake is retained in some lesions but not in others.
- Metastatic disease that progresses despite substantial uptake of radioactive iodine.
- Absence of complete response to treatment after > 600 mCi of cumulative activity of radioactive iodine.
- Evidence of high uptake of fludeoxyglucose (FDG) ^{18}F on positron emission tomography or CT scan; however, importantly, the authors of this review[31] state that this reason alone should not be used to abandon radioactive iodine treatment.

Before deciding whether or not a patient's disease can be described as being RR-DTC, it is important to determine that decreased radioactive iodine uptake is not due to iodine contamination or insufficient TSH.[34]

Radioactive iodine-refractory DTC is a life-threatening form of thyroid cancer with a tendency to progress and metastasise.[14] From published French registry data,[32] the 10-year survival rate and median overall survival (OS) for patients with distant metastases who failed to respond to treatment (no iodine-131 uptake) was 10% and 3 years, respectively. For those who appear to respond to radioactive iodine treatment (iodine-131 uptake) but who did not then attain negative imaging studies, the 10-year survival and median OS was 29% and 6 years, respectively. A separate analysis of patients with lung and/or bone metastases[35] found that 10-year survival and median OS for those who did not have a complete response to treatment with radioactive iodine was 14% and 5 years, respectively. Data from Canada[5] have suggested that the median OS for patients with RR-DTC may be between 2.5 and 3.5 years.

The proportion of patients whose disease becomes refractory to treatment with radioactive iodine is relatively small, and so RR-DTC is described as an ultra-orphan condition.[7,8] Estimates of the proportion of patients who become refractory vary but commonly lie within the range of 5–15%.[7,8,14,16,32,35–37]

As with early-stage DTC, many patients with RR-DTC are initially asymptomatic. As highlighted in a literature review published by Schmidt *et al.*,[31] even patients with distant metastases may have a disease that does not progress for many years; however, as noted by Thyroid Cancer Canada,[5] the cancer continues to progress with no obvious symptoms.

For patients with rapidly progressing disease, which is characterised by symptomatic disease, the symptoms of RR-DTC can be severe, profoundly debilitating and result in patients becoming increasingly dependent on carers.[8] Clinical advice to the Assessment Group (AG) is that the percentage of patients with RR-DTC with rapidly progressing disease is likely to be approximately 25% to 30%. As a result of their symptoms, patients with clinically significant progressive RR-DTC may suffer a poor quality of life and the psychological impact of the disease can also be substantial, resulting in low mood and fatigue.[38] It has also been stated that patients with RR-DTC often experience multiple complications.[39]

Treatment options for patients with radioactive iodine-refractory differentiated thyroid cancer

Radioactive iodine-refractory DTC is typically asymptomatic, but symptoms start to occur as the disease progresses. Symptoms associated with lymph nodes of the neck include difficulty swallowing and/or breathing, pain or sensitivity in the front of the neck or throat, hoarseness or other voice changes, and swelling of the lymph nodes in the neck.[4] Symptoms associated with lung metastases also include swallowing and breathing difficulties.[26] Pain often presents as the principal symptom of metastatic bone involvement.[29,40] Fractures and spinal cord compression are also associated with bone metastases.

Because many treatments, particularly systemic treatments, can have severe side effects and impact significantly on health-related quality of life (HRQoL), clinical advice to the AG is that best supportive care (BSC) tends to be the preferred treatment option, at least until symptoms occur. BSC typically entails TSH suppression therapy and imaging every 3 to 12 months. Palliative radiotherapy and symptom relief are also offered when necessary.

Patients experiencing RR-DTC symptoms and/or patients with rapidly progressing disease are those in need of systemic treatment,[31] as reflected in clinical guidelines.[4,23–25] The aim of systemic treatment for patients with rapidly progressing and/or symptomatic RR-DTC is to gain local disease control in the neck and manage systemic disease.[41] Another important objective of treatment is to prolong survival;[27] however, treatment options for patients with RR-DTC are limited. Within the ESMO guidelines published in 2012,[23] it is stated that chemotherapy should not be given to patients with RR-DTC as it is associated with significant

toxicity with no proven evidence of effectiveness. The authors of these guidelines stated that surgical resection and external beam radiotherapy represented the only therapeutic options and they strongly encouraged enrolment of patients in experimental trials with targeted therapy. Similarly, the authors of the guidelines published by the BTA in 2014[4] only recommended chemotherapy for patients with rapidly progressive, symptomatic RR-DTC who have good performance status (PS), and only when access to targeted therapies in clinical trials is unavailable or when targeted therapies have proved unsuccessful. The authors of the more recent US guidelines published by the American Thyroid Association[24] and NCCN[25] recommend that patients with RR-DTC should usually avoid treatment with chemotherapy. Clinical advice received by the AG is that chemotherapy is rarely used to treat RR-DTC in UK NHS practice.

Targeted therapies were not widely available and were only the subject of clinical trials between 2012 and 2014, when the ESMO guidelines[23] and the BTA guidelines[4] were published. The authors of the BTA guidelines[4] considered the most promising targeted therapies at that time to be lenvatinib and sorafenib.[4] By 2017, the authors of the NCCN guidelines[25] recommended lenvatinib or sorafenib as the treatment of choice for patients with progressive and/or symptomatic disease; lenvatinib is stated to be the 'preferred' option based on a response rate of 65% for lenvatinib, compared with 12% for sorafenib, although these agents have not been directly compared. However, the authors state that the decision should be based on the individual patient, taking into account the likelihood of response and comorbidities.[25] In cases in which lenvatinib or sorafenib are not available or not appropriate, drugs not regulated by the US Food and Drug Administration (FDA) but used in the context of clinical trials are also recommended by the authors of the NCCN guidelines.[25]

Description of technology under assessment

The two interventions under consideration in this MTA are lenvatinib (Lenvima), manufactured by Eisai Ltd, and sorafenib (Nexavar), manufactured by Bayer HealthCare. Both are a type of tyrosine kinase inhibitor (TKI) known as a multikinase inhibitor (MKI).

A brief comparison of the key features of the two interventions is given in *Table 1*. The AG notes that lenvatinib and sorafenib appear to have slightly different mechanisms of action.[42] Both drugs have been approved for treating RR-DTC in the USA[43,44] and Europe,[49,50] with sorafenib being the first of the two agents to be approved in both jurisdictions. In the USA and Europe, the marketing indications for both lenvatinib and sorafenib are for identical patient populations. Approval in the USA and Europe was based largely on evidence from two Phase III randomised controlled trials (RCTs): SELECT,[51] in which lenvatinib was compared with placebo, and DECISION (StuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine-refractory thyrOid caNcer),[52] in which sorafenib was compared with placebo.

Approval for use in NHS Scotland was granted to sorafenib in June 2015[48] and to lenvatinib in September 2016.[38] Both approvals are for the treatment of patients with progressive, locally advanced or metastatic RR-DTC. In NHS Scotland, the use of both lenvatinib and sorafenib is contingent on the continuing availability of Patient Access Scheme (PAS) prices that have been assessed by the PAS Assessment Group.

Sorafenib has been available in England, since July 2016, via the Cancer Drugs Fund (CDF). It is currently funded for all patients with RR-DTC for whom the treating specialist has established that treatment with sorafenib may be beneficial. According to Bayer HealthCare, based on its analysis of notification data from July 2013 to June 2016, sorafenib has become the standard of care for patients for whom systemic treatment is appropriate.[7] Lenvatinib is not currently available to patients treated in the English or Welsh NHS.

TABLE 1 Comparison of the key features of lenvatinib and sorafenib

Feature	Lenvatinib	Sorafenib
Brand name	Lenvima	Nexavar
Manufacturer	Eisai Ltd	Bayer HealthCare
Class of drug	Oral MKI	Oral MKI
Mechanism of action	Targets VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PDGFR alpha, PDGFR beta, RET and KIT[42]	Targets BRAF, RET, VEGFR2 and VEGFR3[42]
US marketing indication	For the treatment of locally recurrent or metastatic, progressive, RR-DTC (15 February 2015)[43]	For the treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment (22 November 2013)[44]
European Union marketing indication	For the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine (28 May 2015)[45]	For the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine (25 January 2015)[46] In addition to RR-DTC, sorafenib is also indicated for treatment of hepatocellular carcinoma and the treatment of advanced renal cell carcinoma[46]
Dose information for treating RR-DTC	24 mg (two 10-mg capsules and one 4-mg capsule) once daily AEs can be managed through dose reduction and treatment is continued until disease progression or unacceptable toxicity[45]	400 mg (two 200-mg tablets) twice daily, taken without food or with a low-fat meal AEs can be managed through dose reduction and treatment is continued until disease progression or unacceptable toxicity[46]
Important identified risks	Important risks highlighted by the EMA[27] include hypertension, proteinuria, renal failure or impairment, hypokalaemia, cardiac failure, posterior reversible encephalopathy syndrome, hepatotoxicity, haemorrhagic events, arterial thromboembolic events, QTc prolongation and hypocalcaemia Further information, including how to manage some of the risks (e.g. the use of hypertensives for hypertension) is provided in the SmPC[46]	Important risks highlighted by the EMA[26] include severe skin AEs; hand–foot syndrome; hypertension; posterior reversible encephalopathy syndrome; haemorrhage including lung haemorrhage, gastrointestinal haemorrhage and cerebral haemorrhage; arterial thrombosis (myocardial infarction); congestive heart failure; squamous cell cancer of the skin; gastrointestinal perforation; symptomatic pancreatitis and increases in lipase and amylase; hypophosphataemia; renal dysfunction; interstitial lung disease-like events; and drug-induced hepatitis Further information, including how to manage some of the risks (e.g. the use of topical therapies, temporary treatment interruption and/or dose modification or treatment discontinuation for hand–foot syndrome) is provided in the SmPC[46]
List price per pack	£1437.00 for a pack of 30 4-mg capsules and £1437.00 for a pack of 30 10-mg capsules[8]	£3576.56 for a pack of 112 200-mg tablets[47]
Cost per year[a]	£52,307[38]	£38,746[48]

AE, adverse event; BRAF, B-type rapidly accelerated fibrosarcoma; EMA, European Medicines Agency; FGFR, fibroblast growth factor receptors; PDGFR, platelet-derived growth factor receptor; QTc, QT corrected interval; RET, rearranged during transfection; SmPC, summary of product characteristics; VEGFR, vascular endothelial growth factor receptor.

a All costs are presented based on the list price and assume that a patient receives the full dose; however, in clinical practice, most patients will not receive the full dose throughout the course of their treatment. Based on clinical trials, median dose intensity has been reported to be approximately 70% for lenvatinib and approximately 80% for sorafenib.

Eisai Ltd[8] has estimated the incidence of patients in England and Wales with RR-DTC who are potentially eligible for treatment with lenvatinib or sorafenib to be approximately 280 each year. Bayer HealthCare[7] has estimated the incidence to be approximately 225 patients per year. The AG notes that the estimates given by the companies differ in how they are calculated. The estimates provided by the companies are reflective of the population defined by the agreed final scope of this appraisal; however, neither estimate appears to account for the fact that lenvatinib and sorafenib are likely to only be preferred for patients with symptomatic and/or rapidly progressing disease. Clinical advice to the AG is that there are no generally agreed definitions of 'symptomatic' or 'rapidly progressive disease' and that, in clinical practice, definition of a patient's disease status depends on individual patient characteristics. Therefore, it is difficult to further segment the population.

Chapter 2 Definition of the decision problem

Decision problem addressed by the Assessment Group

The decision problem for this appraisal, as described in the final scope issued by NICE,[53] is summarised in *Table 2*.

TABLE 2 Decision problem summarised in the final scope issued by NICE[53] and addressed by the AG

Parameter	In the NICE scope[53]	Addressed by the AG
Interventions	Lenvatinib Sorafenib	As per scope
Population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine	As per scope
Comparators	The interventions listed above will be compared with each other BSC	Explore the feasibility of comparing lenvatinib with sorafenib Comparisons of interventions with BSC
Outcomes	The outcome measures to be considered include: • OS • progression-free survival • response rate • adverse effects of treatment • HRQoL	As per scope
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year The reference case stipulates that the time horizon for estimating clinical effectiveness and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from a NHS and Personal Social Services perspective	As per scope
Other considerations	If the evidence allows, consideration will be given to subgroups based on previous treatment with TKIs Guidance will only be issued in accordance with the marketing authorisation. When the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	As per scope

The overall aims and objectives of the assessment

The aim of this research was to assess the clinical effectiveness and cost-effectiveness of lenvatinib versus sorafenib, within their respective EU marketing authorisations,[45,46] for the treatment of patients with RR-DTC. The research objectives are given below:

- To carry out systematic reviews to compare the clinical effectiveness and cost-effectiveness of –
    - treatment with lenvatinib with treatment with sorafenib for RR-DTC
    - treatment with lenvatinib with BSC for RR-DTC
    - treatment with sorafenib with BSC for RR-DTC.
- To develop an economic model to compare the cost-effectiveness of –
    - treatment with lenvatinib with treatment with sorafenib for RR-DTC
    - treatment with lenvatinib with BSC for RR-DTC
    - treatment with sorafenib with BSC for RR-DTC.

Chapter 3 Methods for reviewing clinical effectiveness literature

Search strategy

The AG identified clinical studies and systematic reviews by searching EMBASE, MEDLINE, PubMed and The Cochrane Library from 1999 onwards. All databases were searched on 10 January 2017. Based on the fact that the FDA approved sorafenib for its first indication in 2005, and lenvatinib in 2015, the AG considered that this date span would allow all relevant clinical evidence to be identified. Searches were restricted to publications in English language. The AG did not use any other search filters. The search strategies used by the AG are provided in *Appendix 1*. In addition to the electronic database searches, information on studies in progress was sought (on 16 May 2017) by searching the ClinicalTrials.gov website, the International Clinical Trials Registry Platform and the European Union Clinical Trials Register. The references in the systematic reviews included in the AG's review of systematic reviews, and those listed in the submissions from professional stakeholders that were submitted to NICE, as part of the NICE MTA process, were cross-checked to identify any relevant studies not retrieved from the electronic database searches. Literature search results were uploaded to and managed using EndNote X7.4 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] software.

Study selection

The eligibility criteria listed in *Table 3* were used to identify studies for inclusion in the AG's literature review.

TABLE 3 Eligibility criteria (clinical effectiveness)

Criteria	Inclusion	Exclusion
Patient population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine	Patients with other types of thyroid cancer or diseases
Interventions	Lenvatinib or sorafenib monotherapy (or in combination with BSC)	Lenvatinib or sorafenib in combination with other agents
Comparators	Lenvatinib or sorafenib monotherapy (or in combination with BSC), BSC and placebo	A comparator other than lenvatinib, sorafenib, BSC and placebo
Outcomes	The outcome measures to be considered include OS, progression-free survival, response rate, adverse effects of treatment and HRQoL	No study was excluded based on outcomes
Study design	RCTs, systematic reviews and prospective observational studies	Retrospective cohort studies, case series, case reports, comments, letters, editorials, in vitro, animal and genetic or histochemical studies
Restrictions	English language only	Non-English-language studies

Two reviewers (JH and RH) independently screened all titles and abstracts that were identified in the initial searches (screening stage 1). Based on the titles and abstracts, full-text papers that appeared to be relevant were obtained and assessed for inclusion by the same two reviewers in accordance with the AG's eligibility criteria (screening stage 2). When necessary, discrepancies were resolved by consultation with a third reviewer (NF). At both stages of screening, studies that did not meet the inclusion criteria were excluded, and, at screening stage 2, the reasons for excluding studies were noted.

The eligibility criteria in *Table 3* differ slightly from those specified in the AG's systematic review protocol.[55] The AG, responding to a suggestion from NICE in relation to the final protocol,[55] agreed to include evidence from prospective observational studies that had been submitted to the European Medicines Agency (EMA); however, as only reviewing studies included in the EMA submissions[26,27] would have introduced selection bias, the AG included all prospective observational studies of patients with RR-DTC identified by its searches.

Data extraction and quality assessment strategy

Data relating to RCT study characteristics and outcomes were extracted by one reviewer (NF) and independently checked for accuracy by a second reviewer (YD). Data relating to study characteristics and outcomes of systematic reviews and observational studies were extracted by one reviewer (JH or NF) and independently checked for accuracy by a second reviewer (JG). In all cases, a consensus was reached. Study data reported in multiple publications were extracted and reported as a single study. Data were extracted into tables in Microsoft Word (Microsoft Corporation, Redmond, WA, USA).

As specified in the AG's systematic review protocol,[55] the quality of included RCTs and systematic reviews was assessed according to the criteria set out in the Centre for Review and Dissemination's guidance[56] for undertaking reviews in health care. The quality of the included RCTs was assessed by one reviewer (YD) and independently checked for agreement by a second reviewer (NF). In all cases, a consensus was reached. The quality of the included systematic reviews was assessed by one reviewer (JG) and independently checked for agreement by a second reviewer (YD). When necessary, discrepancies were resolved by consultation with a third reviewer (MR).

Methods of analysis/synthesis

The AG's data extraction and quality assessment results are presented in structured tables and as a narrative summary. Data from RCTs are considered to provide primary clinical effectiveness evidence, with data from systematic reviews and observational studies considered to provide supporting evidence.

As the available evidence did not include two or more RCTs comparing the same intervention, the AG was not able to conduct a meta-analysis of RCT data.

The AG assessed the feasibility of conducting an indirect comparison of effectiveness data (including a comparison to assess effectiveness according to previous treatment with TKIs) by evaluating the clinical and methodological heterogeneity of the included RCTs. Heterogeneity was assessed by comparing (1) trial characteristics, (2) participant characteristics, (3) outcome data and (4) study quality.

Chapter 4 Findings from the systematic review of clinical effectiveness literature

Quantity and quality of research available

Included studies

The process of study selection is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in *Figure 4*. The electronic searches yielded 2358 papers, and six additional references[5–8,57,58] were identified through other sources. In total, the AG included 93 papers[5–8,33,51,52,57–142] reporting on 24 separate studies and reviews: two unique RCTs,[51,52] 13 unique systematic reviews[5–8,33,57,61,93,97,104,127,138,141] and nine unique prospective observational studies.[59,77,78,81,88,101,103,126,135]

Excluded studies

A full list of studies excluded at stage 2 with reasons for exclusion is presented in *Appendix 2*, *Table 32*.

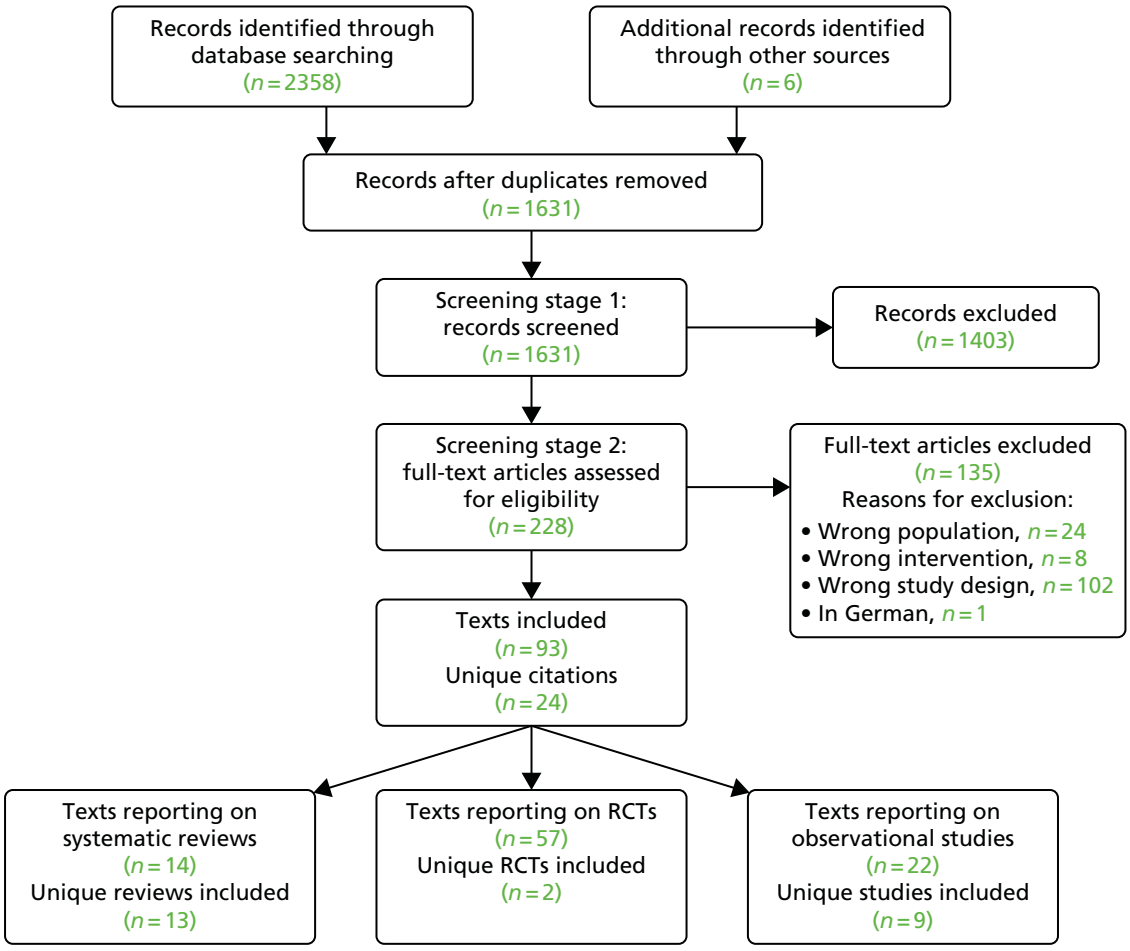

FIGURE 4 The PRISMA flow diagram: studies included in AG's systematic review. Reproduced with permission from Fleeman *et al.*[54] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Evidence from randomised controlled trials

Only two RCTs were identified as relevant for inclusion in the AG's systematic review: SELECT and DECISION. Except when stated otherwise, all information about these two trials has been extracted from the two key trial publications.[51,52]

Trial characteristics

A summary of the characteristics of the two included trials is provided in *Table 4*. Both trials were Phase III, multicentre, double-blind RCTs designed to compare the intervention of interest (lenvatinib or sorafenib)

TABLE 4 Characteristics of SELECT and DECISION

	Study	
Parameter	**SELECT**	**DECISION**
Primary reference	Schlumberger *et al.* 2015[51]	Brose *et al.* 2014[52]
Number of centres	117	81
Stratification factors	Subjects were stratified by age (≤ 65 years or > 65 years), geographical region (Europe, North America or other) and receipt or non-receipt of prior VEGFR-targeted therapy (0 or 1)	Subjects were stratified by age (< 60 years or ≥ 60 years) and geographical region (North America, Europe or Asia)
Country	Centres were distributed as follows: Europe, 60 (51.3%); North America, 31 (26.5%); Asia Pacific, 13 (11.1%); Japan, 6 (5.1%); and Latin America, 7 (6.0%)	18 countries from Europe (59.7%) (Austria, Belgium, Bulgaria, Denmark, France, Germany, Italy, Poland, Russia, Spain, Sweden, the Netherlands and the UK), the USA (17.3%) and Asia (23%) (China, Japan, South Korea and Saudi Arabia)
Recruitment period	5 August 2011 to 4 October 2012	5 November 2009 to 29 August 2012
Participants (*n*)	612 assessed, 392 randomised	556 enrolled, 419 randomised
Intervention dose and schedule	Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) continuous once daily ($n = 261$)	Sorafenib 400 mg (two 200-mg tablets) twice daily for a total daily dose of 800 mg ($n = 207$)
Comparator arm (*n*)	Placebo: 131	Placebo: 210
Primary outcome	PFS, assessed every 8 weeks[a] and determined by blinded independent imaging review conducted by the imaging core laboratory using RECIST 1.1	PFS, assessed every 8 weeks by central independent blinded review using RECIST 1.0
Relevant secondary outcomes	• OS, measured from the date of randomisation until date of death from any cause • Investigator-assessed PFS • ORR (defined as the proportion of subjects who had the best overall response of complete response or partial response as determined by blinded independent imaging review using RECIST 1.1) and related outcomes including duration of response, stable disease, disease control rate and clinical benefit rate • Safety	• OS, measured from the date of randomisation until the date of death from any cause • Investigator-assessed PFS • ORR (defined as the proportion of subjects who had the best overall response of complete response or partial response as determined by blinded independent imaging review using RECIST 1.0) and related outcomes including duration of response, stable disease and disease control rate • Safety • HRQoL
Primary analysis	≥ 214 progression events or deaths	≈267 progression events
Data cut-off points	November 2013, June 2014 and August 2015	August 2012, May 2013 and July 2015

RECIST, Response Evaluation Criteria in Solid Tumours; VEGFR, vascular endothelial growth factor receptor.
a Every 12 weeks in the extended open-label phase of the trial.
Note
Information drawn from Schlumberger *et al.*,[51] Eisai Ltd,[8] Brose *et al.*[52] and Bayer HealthCare.[7]

with placebo. Subjects were randomised in a ratio of 2 : 1 to the intervention and comparator arms of SELECT, whereas they were randomised in a ratio of 1 : 1 in DECISION. In both trials, the primary outcome was progression-free survival (PFS) assessed by blinded independent review. Both trials also reported investigator-assessed PFS. Unless otherwise specified, in the remainder of this AG report on clinical effectiveness, PFS refers to PFS assessed by blinded independent review.

Analysis of clinical efficacy

All efficacy outcomes from both trials, including tumour response evaluations in SELECT, were undertaken using data from the intention-to-treat (ITT) population. Tumour response evaluations in DECISION were undertaken using data from the per-protocol population (i.e. randomised patients who were evaluable for tumour response with imaging data, had received the intervention or placebo as allocated and had no major protocol deviations).

Analysis of safety

Safety analyses for both trials were undertaken using data from the population of patients who were randomised and received at least one dose of study drug and had at least one post-baseline safety evaluation. In SELECT, the numbers of patients included in the ITT and safety populations were identical.

Patients eligible for inclusion

A summary of the criteria describing patient eligibility for entry into SELECT and DECISION is presented in *Appendix 3*, *Table 33*. Both trials only included patients with RR-DTC and who had an Eastern Cooperative Oncology Group (ECOG) PS of 0–2. As highlighted in *Chapter 1*, *Radioactive iodine-refractory differentiated thyroid cancer*, there is no universally agreed definition of RR-DTC. The definitions used to define RR-DTC in the two trials were broadly similar (see *Appendix 3*, *Table 34*, for definitions employed by the trials for RR-DTC).

The main difference in trial eligibility was that SELECT permitted the enrolment of patients who had been previously treated with a vascular endothelial growth factor receptor (VEGFR)-targeted therapy (including sorafenib) and DECISION did not. Age, region and VEGFR-targeted therapy were stratification factors in SELECT, whereas age and region were stratification factors in DECISION.

Dose modifications/interruptions and concomitant therapy

In both trials, the starting dose for treatment with lenvatinib or sorafenib was the licensed dose (24 mg and 800 mg, respectively). Both trials permitted dose modifications or interruptions. The criteria were not stated in the protocol for SELECT but the summary of product characteristics (SmPC)[45] includes a dose/toxicity management plan for lenvatinib. For DECISION, Brose *et al.*[72] stated that dose modifications or interruptions were allowed, based on specific criteria, for grade 2 to grade 3 hand–foot syndrome and other adverse events (AEs).

A summary of the concomitant therapies permitted and prohibited in each trial is presented in *Appendix 3*, *Table 35*. Although neither trial describes BSC for patients in either arm, permitted concomitant therapies could be considered to be BSC and were available to patients in both arms of both trials. The main difference between the two trials is that palliative radiotherapy, which is commonly available as part of BSC in UK NHS clinical practice, was not permitted in either arm of SELECT.

Subgroup analyses

In SELECT, subgroup analyses were prespecified for patients previously treated with a VEGFR-targeted therapy and for those who were not. Both trials also included prespecified subgroup analyses for age, region, sex and histology. Subgroup analyses were prespecified for PFS, OS and objective tumour response rate (ORR) in SELECT but only for PFS in DECISION. Other prespecified subgroup analyses in SELECT were for race and for patients whose TSH level was highest prior to progression. Other prespecified subgroup analyses in DECISION included site of metastasis, FDG take-up, prior radioactive iodine cumulative dosing, tumour burden as measured by number of target or non-target lesions and as measured by the sum of

target diameters. Many other post hoc subgroup analyses were also conducted for both trials (see *Appendix 3*, *Table 37*).

Follow-up, dose intensity and treatment crossover and other subsequent therapy received

At the time of the primary data cut-off points for both trials, OS data were immature. Therefore, for both trials, OS was updated at two subsequent data cut-off points. The median duration of follow-up at each data cut-off point was approximately 17 months at the first data cut-off point in both trials and there were approximately 20 months of additional follow-up in both trials by the final data cut-off point (see *Appendix 3*, *Table 36*).

Patients were eligible to receive treatment (intervention or placebo) in both trials until disease progression. An important feature of both trials is that, on disease progression, patients were unblinded and permitted to cross over from the placebo arm to the active treatment arm. In both trials, patients who crossed over were entered into an open-label extension phase of the same trial. In DECISION, patients who had progressed on sorafenib were also eligible to enter the open-label extension phase of the trial and receive further sorafenib until further disease progression. However, patients who progressed on lenvatinib in SELECT were not permitted to receive additional lenvatinib in the open-label extension phase. Information on treatment crossover and subsequent treatment received is reported in *Table 5*; it is evident that the majority of patients in both placebo arms, and particularly in the placebo arm of SELECT, crossed over to receive lenvatinib or sorafenib.

In addition, some patients received subsequent anti-cancer treatments, not part of the trial protocols, on disease progression (see *Appendix 3*, *Table 39*). In SELECT, at the first data cut-off point (November 2013), 15.7% of patients randomised to lenvatinib and 12.2% of patients randomised to placebo received subsequent treatment. In DECISION, at the first data cut-off point (August 2012), 20.3% of patients randomised to sorafenib and 8.6% of patients randomised to placebo received subsequent treatments. For the most part, subsequent treatment in both trials comprised antineoplastic and immunomodulating agents. The specific antineoplastic and immunomodulating agents were reported only for SELECT, as data were not collected on the specific agents used during the trial follow-up for DECISION. Most commonly, patients received pazopanib (Votrient®, Novartis) (17.1% and 18.8% of patients who received subsequent therapy in the lenvatinib and placebo arms, respectively) and/or sorafenib (14.6% and 12.5% of patients who received subsequent therapy in the lenvatinib and placebo arms, respectively).

TABLE 5 Treatment crossover in SELECT and DECISION (those who entered the extended open-label phase of the trials)

	Study, *n* (%)			
	SELECT		DECISION	
Characteristic	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
Patients who crossed over: first data cut-off point	N/A	109 (83.2)	55 (26.6)[a]	150 (71.4)
Patients who crossed over: second data cut-off point	N/A	115 (87.8)	NR	157 (74.8)
Patients who crossed over: third data cut-off point	N/A	115 (87.8)	NR	158 (75.0)

N/A, not applicable; NR, not reported.

a Patients did not cross over from the sorafenib arm to the placebo arm in DECISION but were permitted to receive additional sorafenib. Data reported here are for those who received additional sorafenib.

Note

Information drawn from Schlumberger *et al.*,[51] Eisai Ltd[8] (including appendix 4), Brose *et al.*[52] and Bayer HealthCare.[7]

Methods used for adjusting for treatment crossover

As patients in both trials were permitted to cross over to receive the intervention drug on disease progression, the OS results are likely to be confounded. The authors of the SELECT publication[51] employed the rank-preserving structural failure time model (RPSFTM) to adjust the OS results for patient crossover. The OS results from DECISION have been adjusted using both the RPSFTM and the iterative parameter estimation (IPE). The unadjusted and adjusted OS analyses have been reported in conference abstracts for SELECT,[87] DECISION[58,68,110] and in the company submissions.[7,8]

As patients were not censored when they received postprogression treatments, the RPSFTM and IPE methods implicitly included all subsequent therapies as an inherent part of the intervention/control treatment effect. In other words, it is assumed that the subsequent therapy administered to patients in each arm of the trial is reflective of the subsequent therapy that would have been offered to patients receiving the same treatment in clinical practice.

The RPSFTM and IPE methods also both rely critically on the 'common treatment effect' assumption, that is, the effect of receiving the experimental treatment is the same when received on diagnosis (i.e. in patients initially randomised to the experimental arm) as it is in treatment switchers (i.e. patients from the control arm who switch to receive the experimental treatment). In practice, it is unlikely that the 'common treatment effect' assumption will ever be completely true; however, it is appropriate to use RPSFTM/IPE methods if the assumption is likely to be approximately true.[143] Clinical advice to the AG was that for both SELECT and DECISION it is reasonable to assume that patients who switched from the placebo arm to receive the experimental treatment (i.e. lenvatinib/sorafenib) would experience the same treatment effect as patients who were originally randomised to the experimental arm.

In addition to the assumptions that are common to both the RPSFTM and the IPE methods, the IPE method also assumes that survival times follow a parametric distribution. To implement this method, a suitable parametric model must be identified, which can be problematic. The AG has been unable to identify information on how the IPE analysis was carried out using data from DECISION, including details of the parametric model chosen, and so is not able to comment on the suitability of this method.

Generally, the key assumption of a 'common treatment effect' that underpins RPSFTM appears to be valid, and because a large number of placebo patients crossed over to active treatment in both trials, the AG is of the opinion that RPSFTM is the most suitable method for adjusting for treatment switching in SELECT and DECISION. However, a caveat to the use of the RPSFTM-adjusted OS results for both trials is that differences in poststudy (postprogression) anti-cancer treatments administered to patients in each treatment arm are not accounted for in this analysis.

Participant characteristics

Overall, the baseline characteristics of patients included in SELECT and in DECISION were balanced between treatment arms (*Table 6*). Nevertheless, there are a few notable differences between the treatment arms and also across the trials.

In SELECT, there was a lower proportion of males in the lenvatinib arm (47.9%) than in the placebo arm (57.3%). The median time from diagnosis of DTC to randomisation was shorter in the lenvatinib arm than in the placebo arm (66.0 vs. 73.9 months). Compared with the placebo arm, a smaller proportion of patients in the lenvatinib arm had metastases in the lung [86.6% (lenvatinib) vs. 94.7% (placebo)] or liver [16.5% (lenvatinib) vs. 21.4% (placebo)].

In DECISION, a higher proportion of patients in the sorafenib arm had metastases in the lymph node (54.6%) or pleura (19.3%) than in the placebo arm (48.1% and 11.4%, respectively). There was a higher proportion of males in the sorafenib arm (50.2%) than in the placebo arm (45.2%).

TABLE 6 Participant characteristics in SELECT and DECISION

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
Age (years), median (minimum to maximum)	64 (27 to 89)	61 (21 to 81)	63 (24 to 82)	63 (30 to 87)
Male, *n* (%)	125 (47.9)	75 (57.3)	104 (50.2)	95 (45.2)
Race, *n* (%)				
White	208 (79.7)	103 (78.6)	123 (59.4)	128 (61.0)
Black of African American	4 (1.5)	4 (3.1)	6 (2.9)	5 (2.4)
Asian	46 (17.6)	24 (18.1)	47 (22.7)	52 (24.8)
Other	3 (1.2)	0	2 (1.0)	2 (1.0)
Missing or uncodeable			29 (14.0)	23 (11.0)
Region, *n* (%)				
Europe	131 (50.2)	64 (48.9)	124 (59.9)	125 (59.5)
North America	77 (29.5)	39 (29.8)	36 (17.4)	36 (17.1)
Other	53 (20.3)	28 (21.4)	47 (22.7)	49 (23.3)
Time from diagnosis of DTC to randomisation (months), median (range)	66 (0.4–573.6)	73.9 (6.0–484.8)	66.2 (3.9–362.4)	66.9 (6.6–401.8)
ECOG PS, *n* (%)				
0	144 (55.2)	68 (51.9)	130 (62.8)	129 (61.4)
1	104 (39.8)	61 (46.6)	69 (33.3)	74 (35.2)
2	12 (4.6)	2 (1.5)	7 (3.4)	6 (2.9)
3	1 (0.4)	0	0	0
Not available	0	0	1 (0.5)	1 (0.5)
Histology, *n* (%)				
Papillary	132 (50.6)	68 (51.9)	118 (57.0)	119 (56.7)
Poorly differentiated	28 (10.7)	19 (14.5)	24 (11.6)	16 (7.6)
Follicular, not Hürthle cell	53 (20.3)	22 (16.8)	13 (6.3)	19 (9.0)
Hürthle cell	48 (18.4)	22 (16.8)	37 (17.9)	37 (17.6)
Other	0	0	2 (1.0)	5 (2.4)
Missing or non-diagnosed	0	0	13 (6.3)	14 (6.7)
Metastases, *n* (%)				
Locally advanced	4 (1.5)	0	7 (3.4)	8 (3.8)
Distant	257 (98.5)	131 (100)	200 (96.6)	202 (96.2)
Metastases site, *n* (%)				
Lung	226 (86.6)	124 (94.7)	178 (86.0)	181 (86.2)
Lymph node	138 (52.9)	64 (48.9)	113 (54.6)	101 (48.1)
Bone	104 (39.8)	48 (36.6)	57 (27.5)	56 (26.7)
Pleura	46 (17.0)	18 (13.7)	40 (19.3)	24 (11.4)
Head and neck	NR	NR	33 (15.9)	34 (16.2)
Liver	43 (16.5)	28 (21.4)	28 (13.5)	30 (14.3)

TABLE 6 Participant characteristics in SELECT and DECISION (*continued*)

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
Thyroid surgery, *n* (%)	261 (100)	131 (100)	207 (100)	208 (99.0)
Median cumulative radioiodine activity (mCi)	350		400	376
Target tumour size, *n* (%)				
< 35	65 (24.9)	28 (21.4)	44 (21.3)	51 (24.3)
36–60	72 (27.6)	32 (24.4)	34 (16.4)	48 (22.9)
61–92	63 (24.1)	34 (26.0)	51 (24.6)	34 (16.2)
> 92	61 (23.4)	37 (28.2)	78 (37.7)	77 (36.7)
Prior VEGFR-targeted therapy, *n* (%)	66 (25.3)	27 (20.6)	0	0

mCi, millicurie; NR, not reported.
Note
Information drawn from Eisai Ltd,[8] Schlumberger *et al.*,[51] EMA,[27] Brose *et al.*[52] and Bayer HealthCare[7] (appendix 7.5, table 12).

As previously highlighted, patients in SELECT could have been previously treated with a VEGFR-targeted therapy (including sorafenib) prior to trial entry whereas patients in DECISION could not. Approximately one-quarter (23.7%) of patients in SELECT had received prior treatment with a VEGFR-targeted therapy. In the lenvatinib arm, of 66 patients previously treated with a VEGFR-targeted therapy, 51 patients (77.2%) were treated with sorafenib. In the placebo arm, of 27 patients previously treated with a VEGFR-targeted therapy, 21 patients (77.8%) were treated with sorafenib. Other VEGFR-targeted therapies used prior to trial entry in SELECT included sunitinib (Sutent®, Pfizer) and pazopanib. The median duration of any prior therapy was ≈11 months in both arms.

A higher proportion of enrolled patients were from North America in SELECT than in DECISION (29.6% vs. 17.3%, respectively) and a lower proportion of patients were from Europe in SELECT than in DECISION (49.7% vs. 59.7%, respectively). A greater proportion of patients were white in SELECT (79.3%) than in DECISION (60.2%). A higher proportion of patients had bone metastases in SELECT than in DECISION (38.8% vs. 27.1%, respectively).

Comparison of assessments of risk of bias

A summary of the risk-of-bias assessments for both trials is reproduced in *Appendix 3*, *Table 48*. Overall, the AG considered the risk of bias to be low in both trials.

Consideration of proportional hazards assumption

Cox proportional hazards (PHs) modelling was used to generate PFS, unadjusted OS and adjusted OS hazard ratios (HRs) from data collected during SELECT and DECISION. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time within each trial. The AG assessed the validity of the PH assumption for all analyses, when possible, provided in the submissions from Eisai Ltd[8] and Bayer HealthCare[7] that included a HR result (see *Appendix 6* for methods and results). The AG concluded that the PH assumption was not valid for PFS, unadjusted OS or RPSFTM-adjusted OS in SELECT or for PFS or RPSFTM-adjusted OS in DECISION. This means that the majority of the survival HRs generated using data from SELECT and DECISION and, consequently, statements about the statistical significance of results should be interpreted with caution.

Overall survival

A summary of the unadjusted and adjusted OS findings from the most recent data cut-off points from both trials is presented in *Table 7*. The findings for all data cut-off points are summarised in *Appendix 3*, *Table 38*.

TABLE 7 Overall survival findings from SELECT and DECISION

Outcome	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
Data cut-off point[a]	Third data cut-off point (August 2015)		Third data cut-off point (July 2015)	
Deaths, *n* (%)	121 (46.4)	70 (53.4)	103 (49.8)	109 (51.9)
OS (months), median (95% CI)	41.6 (31.2 to NE)	34.5 (21.7 to NE)	39.4 (32.7 to 51.4)	42.8 (34.7 to 52.6)
Unadjusted HR (95% CI); *p*-value	0.84 (0.62 to 1.13); nominal $p = 0.2475$		0.92 (0.71 to 1.21); one-sided $p = 0.28$	
RPSFTM-adjusted HR (95% CI); *p*-value, cox method	NR		0.77 (0.58 to 1.02); NR	
RPSFTM-adjusted HR (95% CI); *p*-value, bootstrapping method	0.54; nominal $p = 0.0025$ (0.36 to 0.80)		0.77 (0.42 to 1.79); NR	
IPE-adjusted HR (95% CI); *p*-value, cox method	N/A		0.80 (0.61 to 1.05); NR	
IPE-adjusted HR (95% CI); *p*-value, bootstrapping method	N/A		0.80 (0.48 to 1.71); NR	

CI, confidence interval; N/A, not applicable; NE, not estimable; NR, not reported.
a See *Chapter 5*, *Survival modelling*, for details of the data cut-off points used in the AG's economic model.
Note
Information drawn from Eisai Ltd[8] (from tables 6 and 8 of the submission) and Bayer HealthCare[7] (from pages 28 to 29 of the submission).

In both trials, there was no statistically significant difference in unadjusted OS between trial arms. However, when RPSFTM was used, patients in the lenvatinib arm had a statistically significant improvement in OS when compared with patients in the placebo arm in SELECT. The difference in OS between sorafenib and placebo was not reported to be statistically significant when using either the RPSFTM or IPE method in DECISION.

Progression-free survival

In both trials, the primary outcome was PFS by blinded independent review. The findings for PFS reported in SELECT and DECISION are summarised for the first data cut-off points (November 2013 and August 2012, respectively) in *Table 8* because this was the only data cut-off point for which PFS results had been published for both trials.

In SELECT, there was a median improvement in PFS (blinded independent review) of 14.7 months with lenvatinib when compared with placebo. In DECISION, there was a 5-month median improvement in PFS (blinded independent review) with sorafenib when compared with placebo. The differences in median PFS assessed by investigators were marginally decreased in SELECT (12.9 months) and marginally increased in DECISION (5.4 months). However, the HRs in both trials were similar to those from the assessments by blinded independent review.

The SELECT trial is the only trial that also reports PFS for another data cut-off point.[85,86] This was available for investigator-assessed PFS at the third data cut-off point (August 2015). Compared with the first data cut-off point, median PFS was reported to be slightly higher in the lenvatinib arm at the third data cut-off point (19.4 months), but the median PFS remained the same in the placebo arm (3.7 months), a difference of 15.7 months. However, for both data cut-off points, the HR between arms was identical (0.24) and reported to be statistically significant ($p < 0.001$).

The findings for all data cut-off points are summarised in *Appendix 3*, *Table 41*.

TABLE 8 Progression-free survival findings from SELECT and DECISION

Outcome	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
	First data cut-off point (November 2013)		First data cut-off point (August 2012)	
PFS by blinded independent review				
Events, *n* (%)	93 (35.6)	109 (83.2)	113 (54.6)	137 (65.2)
Died before progression, *n* (%)	14 (5.4)	4 (3.1)	NR	NR
PFS (months), median (95% CI)	18.3 (15.1 to NE)	3.6 (2.2 to 3.7)	10.8 (NR)	5.8 (NR)
Stratified HR (95% CI);[a] *p*-value	0.21 (0.14 to 0.31); < 0.001		0.59 (0.45 to 0.76); < 0.0001	
Investigator-assessed PFS				
Events, *n* (%)	91 (34.9)	104 (79.4)	140 (67.6)	184 (87.6)
Died before progression, *n* (%)	16 (6.1)	6 (4.6)	NR	NR
PFS (months), median (95% CI)	16.6 (4.8 to NE)	3.7 (3.5 to NE)	10.8 (NR)	5.4 (NR)
Stratified HR (95% CI);[a] *p*-value	0.24 (0.16 to 0.35); < 0.001		0.49 (0.39 to 0.61); < 0.0001	

CI, confidence interval; NE, not estimable; NR, not reported.

a Stratification factors for SELECT were age (≤ 65 years or > 65 years), geographical region (Europe, North America or other) and receipt or non-receipt of prior VEGFR-targeted therapy (0 or 1). Stratification factors in DECISION were age (< 60 years or ≥ 60 years) and geographical region (North America, Europe or Asia).

Note

Information drawn from Schlumberger *et al.*[51] and Brose *et al.*,[52] with additional data from Eisai Ltd[8] and Bayer HealthCare.[7]

Objective tumour response

The findings for objective tumour response are reported in *Appendix 3*, *Table 42*. In both trials, the tumour response assessment was conducted by blinded independent review at the first data cut-off point and favoured patients in the intervention arms compared with patients in the placebo arms. It is noticeable that the difference in ORR between the intervention and placebo arms was much greater for patients treated with lenvatinib in SELECT (63.2%) than for those treated with sorafenib in DECISION (11.7%). This is attributable to the much higher proportion of patients who were treated with lenvatinib and had a partial response in SELECT than the proportion of patients treated with sorafenib in DECISION. Complete responses were only reported for patients treated with lenvatinib, albeit there were very few patients (1.5%). ORR was statistically significantly improved in both trials for patients treated with either lenvatinib or sorafenib when compared with placebo.

The objective tumour response evaluations for SELECT were conducted using an ITT analysis. In DECISION, patients for whom it was not possible to evaluate a tumour response were excluded from the analysis (as per the requirements of a per-protocol analysis). If all patients are included in the evaluations using ORR data from DECISION, the ORR is marginally decreased in both arms: 11.6% for sorafenib and 0.5% for placebo.

Time to response was reported only for SELECT. The median time to response was 2.0 months for patients treated with lenvatinib compared with 5.6 months for patients in the placebo arm. The median duration of response was not estimable for patients in SELECT; however, for those treated with lenvatinib, the restricted mean was 17.34 months. Time to response was not reported in DECISION, but the median duration of response was 10.2 months for patients treated with sorafenib.

Both trials also assessed disease control rates (complete response + partial response + stable disease), and SELECT reported clinical benefit rate (complete response + partial response + durable stable disease). In each trial, the findings were statistically significantly in favour of lenvatinib or sorafenib compared with placebo. However, comparisons between trials cannot be easily made as the definition of disease control rate differed across trials because of differences in the length of stable disease required for control. SELECT required a stable disease of ≥ 7 weeks whereas DECISION required a length of ≥ 4 weeks; however, both trials did report the proportion of patients with stable disease of ≥ 6 months. This was similar in the placebo arms of both trials (SELECT, 29.8%; DECISION, 33.2%), whereas in the intervention arms, it was 15.3% for patients treated with lenvatinib and 41.8% for patients treated with sorafenib. Therefore, a clinical benefit at 6 months was reported by 79.5% of patients treated with lenvatinib compared with 31.3% of patients who received the placebo in SELECT, and 54.0% patients treated with sorafenib compared with 33.7% who received the placebo in DECISION. In the submission from Bayer HealthCare,[7] it is noted that most sorafenib-treated patients (77%) experienced target lesion tumour shrinkage (compared with 28% of patients in the placebo arm).

Safety findings

Safety data from SELECT and DECISION were reported for the first data cut-off point (November 2013 and August 2012, respectively). For the individual types of AEs experienced by patients, the published paper for SELECT presented data for treatment-related AEs whereas the published paper for DECISION presented data for any treatment-emergent AEs. Therefore, data for specific types of treatment-emergent AEs were extracted from the pharmaceutical company submission (Eisai Ltd[8]) for SELECT.

All-grade and grade ≥ 3 adverse events

Nearly all of the patients who received lenvatinib or sorafenib reported an AE, and ≈90% of patients who received placebo reported an AE. AEs that were reported by ≥ 30% of patients and grade ≥ 3 AEs that were reported by ≥ 1.5% of patients in any of the arms are summarised in *Appendix 3*, *Tables 44* and *45*. All types of AEs were more common in patients treated with lenvatinib or sorafenib than in patients in the placebo arms of both trials. Hand–foot syndrome was reported by approximately three-quarters of patients in DECISION. Approximately two-thirds of patients reported all-grade hypertension or diarrhoea when treated with lenvatinib in SELECT, similar to the proportion treated with sorafenib reporting all-grade diarrhoea or alopecia in DECISION. Weight loss was reported by approximately half of all patients treated with either lenvatinib or sorafenib. By far the most common grade ≥ 3 AEs for patients treated with lenvatinib and sorafenib were hypertension (> 40%) and hand–foot syndrome (> 20%), respectively.

Serious adverse events (including fatal adverse events)

Serious adverse events (SAEs) reported in SELECT and DECISION are summarised in *Appendix 3*, *Table 45*. In SELECT, approximately half of the patients in the lenvatinib arm reported a SAE. Just over one-third of patients reported a SAE in the sorafenib arm of DECISION. Approximately one-quarter of patients in the placebo arms of both trials reported a SAE. The only SAE reported by ≥ 2% of patients in both trials was dyspnoea, which was at least as common for patients who received placebo as for those who received lenvatinib or sorafenib. The most common SAEs (reported by ≥ 3% of patients) reported for patients treated with lenvatinib in SELECT were pneumonia and hypertension. The most common SAEs (reported by ≥ 3% of patients) reported by patients treated with sorafenib in DECISION were secondary malignancy and pleural effusion.

Deaths from AEs were reported for 7.7% of patients treated with lenvatinib and 4.6% of patients in the placebo arm in SELECT. Fatal AEs in DECISION were reported for 5.8% of patients treated with sorafenib and 2.9% of patients in the placebo arm.

Treatment-related adverse events

A summary of treatment-related AEs is presented in *Appendix 3*, *Table 46*. A very high proportion of all-grade AEs (≥ 96%) were considered to be related to treatment with lenvatinib or sorafenib. The proportion of all-grade AEs considered to be treatment related was high (> 50%) in the placebo arms of both trials.

In SELECT, the causes of death considered to be treatment related in the lenvatinib arm were one case each of pulmonary embolism, haemorrhagic stroke and general deterioration of physical health; three cases were reported as deaths or sudden deaths (not otherwise specified). DECISION was the only trial in which a patient in the placebo arm was considered to have died because of a treatment-related AE. The cause of death for this patient was subdural haematoma. The cause of death for a patient in the sorafenib arm that was considered to be treatment related was myocardial infarction.

Timing of adverse events

In both trials, there have been subsequent analyses of the timing of AE occurrences in the treatment cycle reported. For SELECT, Haddad *et al.*[91] reported the incidence and timing of five AEs: proteinuria, diarrhoea, fatigue/asthenia/malaise, rash and hand–foot syndrome. Hypertension was a notable AE omitted from the analysis. For DECISION, detailed analysis of the AE occurrence patterns in patients is published in a peer-reviewed paper by Worden *et al.*[139] Findings from the two trials cannot be easily compared because Haddad *et al.*[91] reported their findings as median time to first onset and median time to last resolution, whereas Worden *et al.*[139] reported the proportion of AEs occurring during each cycle. The AEs reported included hand–foot syndrome, rash/desquamation, diarrhoea, fatigue, hypertension, weight loss, increased TSH levels and hypocalcaemia. Increased TSH levels were described as a 'study-specific' AE, with a maximum severity of grade 1; this AE was reported by 69 patients (33.3%) treated with sorafenib.[139]

In SELECT, Haddad *et al.*[91] found that generally AEs for patients treated with lenvatinib occurred early in the treatment process and were resolved. Median time to onset for patients treated with lenvatinib ranged from 3.0 weeks with fatigue/asthenia/malaise to 12.1 weeks with diarrhoea. With regard to resolution, this ranged from a median of 5.9 weeks with rash to a median of 20.0 weeks with hand–foot syndrome.

In DECISION, Worden *et al.*[139] found that in patients treated with sorafenib, the incidence of AEs was usually highest in the first cycle or the first two cycles. Severity tended to diminish with each cycle (over the first nine cycles). The prevalence of AEs (defined as the number of patients with a new or continuing AE during a treatment cycle) tended to remain stable. Diarrhoea and TSH were notable exceptions in that prevalence steadily increased over the first five or six cycles, at which point the prevalence peaked. Only weight loss, which was primarily grade 1 or grade 2 and highest in the first four cycles, tended to increase in severity over time (from grade 1 to grade 2: a greater proportion of patients experienced grade 2 toxicity in cycle 9 compared with cycles 1 and 2). The authors noted that in general, AEs with sorafenib were manageable over time following dose modification and/or concomitant medications, such as antidiarrhoeals, antihypertensives or dermatological preparations.

Dose modifications

Dose modifications as a result of AEs were more common for patients treated with lenvatinib and sorafenib than for those who received placebo (*Table 9*). It is of note that the incidence of dose interruptions with lenvatinib in SELECT was higher than with sorafenib in DECISION. The incidence of dose interruptions and dose reductions were lower in the placebo arm of SELECT than in the placebo arm of DECISION.

TABLE 9 Dose modifications because of an AE in SELECT and DECISION

	Study, *n* (%)			
	SELECT		DECISION	
Outcome	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 209)
Dose interruptions because of an AE	215 (82.4)	24 (18.3)	137 (66.2)	54 (25.8)
Dose reductions because of an AE	177 (67.8)	6 (4.6)	133 (64.3)	19 (9.1)
Discontinued treatment because of an AE	43 (16.5)	6 (4.6)	39 (18.8)	8 (3.8)

Note
Information drawn from Schlumberger *et al.*[51] and Brose *et al.*[52]

It is reported that, in SELECT, the most common AEs developing during treatment that led to a dose interruption or reduction among patients receiving lenvatinib were diarrhoea (22.6%), hypertension (19.9%), proteinuria (18.8%) and decreased appetite (18.0%). It is also noted that four patients in the lenvatinib arm (1.5%) required dose adjustments owing to hypocalcaemia. In the submission from Eisai Ltd,[8] it is further noted that 1.1% of patients discontinued treatment because of hypertension and 1.1% of patients discontinued because of asthenia. In DECISION, it is reported that hand–foot syndrome was the most common reason for sorafenib dose interruptions (26.6%), reductions (33.8%) and withdrawals (5.3%).

Health-related quality-of-life findings

It was reported in the European Public Assessment Report (EPAR)[27] that, although HRQoL data were not collected in the randomised part of SELECT,[51] HRQoL would be assessed in 30 patients who participated in the open-label extension phase of the trial. The AG is unaware of whether or not these findings have been published.

For DECISION, HRQoL was reported in a conference abstract by Schlumberger *et al.*[120] More detailed HRQoL results were also reported in the submission from Bayer HealthCare.[7] Cancer-specific HRQoL was measured using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire[144] and general health status was measured using the generic EuroQol-5 Dimensions, three-level version (EQ-5D-3L) and the EuroQol-5 Dimensions (EQ-5D) visual analogue scale (VAS).[145] The FACT-G questionnaire is a validated 27-item questionnaire designed to assess the following dimensions in cancer patients: physical well-being, social/family well-being, emotional well-being and functional well-being. The FACT-G total score ranges from 0 to 108 points, with higher scores representing a better HRQoL. Similarly, the EQ-5D is a validated instrument in which higher scores represent better health status.

All questionnaires were self-administered at baseline and day 1 of every 28-day cycle. The overall questionnaire completion rate during the trial was reported by the authors to be 96%.[120] However, the actual number of patients completing the questionnaires reduces with each cycle because only patients with progression-free disease were asked to complete the questionnaires. Thus, for example, as shown in the submission from Bayer HealthCare[7] by the response to one of the physical well-being questions, by cycle 13 the number of patients who responded was 87: 40.1% of all patients enrolled into the trial.

Functional Assessment of Cancer Therapy – General

Minimally important differences in the FACT-G total score (i.e. a difference considered to be clinically meaningful) have been reported to range between 3 and 7 points.[144] At baseline, it was reported[7,120] that FACT-G scores were comparable to a normative adult cancer population, the mean scores being 81 points [standard deviation (SD) 15 points] in the sorafenib arm and 82 points (SD 14 points) in the placebo arm. However, at the first assessment (cycle 2, day 1), the score for the sorafenib arm had fallen to 76 points (SD 15 points), whereas the score in the placebo arm remained very similar to baseline. The authors of the conference abstract[120] reported that the scores in the sorafenib arm thereafter remained similar to the scores at the first assessment, whereas the scores remained similar to the baseline scores in the placebo arm. A mixed linear model estimated that, compared with placebo, the FACT-G score was 3.45 points lower in the sorafenib arm ($p = 0.0006$), representing a clinically meaningful difference between arms in favour of the placebo arm. The authors attributed the diminished HRQoL score to AEs. Indeed, the submission from Bayer HealthCare[7] noted that in response to the FACT-G physical well-being domain question 'I am bothered by side effects', the proportion of patients in the sorafenib arm who replied 'quite a bit' or 'very much' increased from 1.5% at cycle 1 to 29.6% at cycle 2. However, this proportion gradually diminished over time: it was 16.8% by cycle 6 and 8.0% by cycle 13.

EuroQol-5 Dimensions index and visual analogue scale

For UK utility scores, a change of 0.10 points on the EQ-5D index has been reported by Pickard *et al.*[146] to be clinically meaningful for all cancers (using ECOG PS as the anchor). Similarly, the same study reported a change of at ≥ 7 points on the VAS to be clinically meaningful.[146] It was reported in DECISION[7,120] that the patterns for EQ-5D index and VAS were similar to that of the FACT-G; after the first assessment, the scores

in the sorafenib arm were lower than the scores in the placebo arm. Although the between-arm differences were statistically significant ($p < 0.0001$ for both EQ-5D index and VAS), the treatment effects (–0.07 and –6.75, respectively) were of a small magnitude and did not reach the threshold for a clinically meaningful difference. It is reported in the submission from Bayer HealthCare[7] that dimensions in the EQ-5D index that are sensitive to AEs include mobility, usual activities and pain/discomfort.

Subgroup analyses from randomised controlled trials

Only subgroup analyses considered by the AG to be of direct relevance to the decision problem have been reported in the remainder of this report. The AG considered the following subgroup analyses to be relevant (with rationale given):

- patients previously treated and not previously treated with TKIs (prespecified subgroup in the NICE scope[53] and AG decision problem)
- patients with and without symptomatic disease at baseline (as highlighted in *Chapter 1*, *Treatment options for patients with radioactive iodine-refractory differentiated thyroid cancer*, systemic treatment is recommended for patients who have symptomatic disease)
- analyses of subgroups that were prespecified in the trials and in which there appeared to be differences in baseline characteristics within or across trials (as differences in baseline characteristics may influence results).

As previously highlighted, the AG concluded that the assumption of PH does not hold in any of the analyses that it was able to check other than unadjusted OS in DECISION. This means that the majority of the survival HRs generated using data from SELECT and DECISION and, consequently, statements about the statistical significance of results should be interpreted with caution.

Patients previously treated and patients not previously treated with tyrosine kinase inhibitors

Subgroup analyses have been reported for patients previously treated with a TKI (e.g. VEGFR-targeted therapy) in SELECT but only for PFS and ORR.[51,105,106] No patients in DECISION had received prior treatment with a TKI.

Results from subgroup analyses using data from SELECT[51,105,106] showed that PFS was statistically significantly longer for patients treated with lenvatinib compared with placebo for patients previously treated with VEGFR-targeted therapy (including sorafenib) (*Table 10*). For patients who were VEGFR-targeted therapy naive, PFS was also statistically significantly longer for patients treated with lenvatinib compared with placebo.

TABLE 10 Progression-free survival findings in patients previously treated and not previously treated with VEGFR-targeted therapy in SELECT: first data cut-off point (November 2013)

	Treatment with VEGFR-targeted therapy			
	Prior treatment		No prior treatment	
Outcome	Lenvatinib ($N = 66$)	Placebo ($N = 27$)	Lenvatinib ($N = 195$)	Placebo ($N = 104$)
Events, *n* (%)	31 (47.0)	25 (92.6)	76 (39.0)	88 (84.6)
Median PFS (months)	15.1	3.6	18.7	3.6
HR (95% CI)	0.22 (0.12 to 0.41)		0.20 (0.14 to 0.27)	

CI, confidence interval.
Note
Information drawn from Schlumberger *et al.*[51] (from figure S1 in the supplementary appendix).

Compared with patients in the placebo arm, ORR was statistically significantly improved for patients treated with lenvatinib whether or not they had been previously treated with a VEGFR-targeted therapy (see *Appendix 3*, *Table 47*).[51,105,106] In both subgroups, ORRs were similar to the ORRs observed in the overall trial population (lenvatinib 64.8% and placebo 1.5%).

Newbold *et al.*[105,106] reported that any all-grade and grade ≥ 3 AEs were similar in the two subgroups of patients receiving lenvatinib (prior VEGFR-targeted therapy 100.0% and 87.9%, respectively; no prior VEGFR-targeted therapy 99.5% and 86.7%, respectively). However, SAEs were more common in the lenvatinib arm among patients who had received prior VEGFR-targeted therapy (60.6%) than among those who had not (50.8%). For patients in the placebo arm, the opposite was the case, with SAEs being less common among patients who had received prior VEGFR-targeted therapy (18.5%) than among those who had not (25.0%).

Patients who had not received prior VEGFR-targeted therapy were treated with more cycles of lenvatinib (median 16 cycles) than those who had received prior VEGFR-targeted therapy (median 12.5 cycles). The proportion of patients who had at least one lenvatinib dose reduction was also similar between subgroups (prior VEGFR-targeted therapy 81.8% and no VEGFR-targeted therapy 86.7%). Patients with no prior VEGFR-targeted therapy had an earlier median time to first dose reduction (8.9 weeks) than patients with prior VEGFR-targeted therapy (14.8 weeks). Patients with no prior VEGFR-targeted therapy also had a lower median daily dose of lenvatinib than those with prior VEGFR-targeted therapy (16.1 vs. 20.1 mg, respectively).

Patients with and without symptomatic disease at baseline

Subgroup analyses were not conducted for patients with symptomatic or asymptomatic disease at baseline in SELECT. In DECISION, the median PFS for patients who were retrospectively categorised as being symptomatic at baseline was longer for patients who were asymptomatic than those who were symptomatic in the placebo arm but was similar in the intervention arm (*Table 11*). Patients were classified as being symptomatic if they had symptoms/findings that were consistent with RR-DTC reported in the medical history or pre-treatment AE data set at trial entry.[113,119] It is noted in the EPAR[26] for sorafenib that ≈20% of patients had symptoms that were likely to be related to thyroid cancer at baseline.

Bayer HealthCare[7] has stated that although tumour shrinkage was not always sufficient to be confirmed as an objective response for some patients, it was often sufficient to alleviate symptoms. Further evidence has not been presented to support this statement.

Safety analyses for patients with symptomatic or asymptomatic disease at baseline have not been reported in SELECT or DECISION.

TABLE 11 Progression-free survival findings in symptomatic and asymptomatic patients in DECISION: first data cut-off point (August 2012)

	Symptom status			
	Symptomatic (≈20%)		Asymptomatic (≈80%)	
Outcome	Sorafenib	Placebo	Sorafenib	Placebo
Events, *n* (%)	NR	NR	NR	NR
Median PFS (months)[a]	10.7	3.6	10.8	7.2
HR (95% CI)	0.386 (0.207 to 0.720)		0.602 (0.448 to 0.807)	

CI, confidence interval; NR, not reported.
a Reported in source documents in days; converted to months by dividing by 365.25 and multiplying by 12.
Note
Information drawn from Bayer HealthCare[7] (from appendix 7.3) and the EPAR for sorafenib.[26]

Other subgroup analyses of interest

Some OS subgroup analyses in SELECT have been reported in conference abstracts.[67,73,82,89] No OS subgroup analyses have been reported using data from DECISION. For OS (first data cut-off point in November 2013) in SELECT, it has been reported that:

- There was no statistically significant difference in OS between older and younger lenvatinib-treated patients [HR 0.78, 95% confidence interval (CI) 0.49 to 1.26; $p = 0.304$] but there was a statistically significant difference in the placebo arm, favouring younger patients (HR 0.48, 95% CI 0.27 to 0.85; $p = 0.010$).[67,73]
- Median OS was not reached in either arm in patients treated in North America.[89]
- A statistically significant OS advantage was observed in patients with FTC treated with lenvatinib compared with placebo (HR 0.41, 95% CI 0.18 to 0.97).[82]

In addition to the subgroup analyses, Haddad *et al.*[91] found from a post hoc exploratory multivariate analysis of SELECT (first data cut-off point) that ECOG PS and histology (favouring FTC vs. PTC) were statistically significantly associated with OS.

For PFS, all prespecified and some post hoc subgroup analyses (first data cut-off points) have also been reported in the appendix to the primary published paper for SELECT[51] and in the published paper for DECISION.[52] The results for both trials showed that for all subgroups, PFS favoured lenvatinib or sorafenib versus placebo. In the majority of instances, the differences were statistically significant. Regarding PFS for prespecified subgroup analyses, the following results are noted:

- The effect was statistically significantly in favour of lenvatinib (compared with placebo) for patients aged ≤ 65 or > 65 years in SELECT; the effect was statistically significantly in favour of sorafenib (compared with placebo) for patients aged < 60 or ≥ 60 years in DECISION.
- The effect was statistically significantly in favour of lenvatinib (compared with placebo) and for sorafenib (compared with placebo) for males and females in SELECT and DECISION.
- The effect was statistically significantly in favour of lenvatinib (compared with placebo) for patients with PTC, poorly differentiated carcinoma, FTC or Hürthle cell carcinoma in SELECT; the effect was statistically significantly in favour of sorafenib (compared with placebo) for patients with PTC or Hürthle cell carcinoma but not for those with FTC or poorly differentiated carcinoma in DECISION.
- The effect was statistically significantly in favour of lenvatinib (compared with placebo) for patients classified as white or Asian in SELECT; no subgroup analyses have been presented for race in DECISION.
- The effect was statistically significantly in favour of lenvatinib (compared with placebo) for patients treated in Europe and North America or other regions in SELECT; the effect was statistically significantly in favour of sorafenib (compared with placebo) for patients treated in Europe or Asia but not for patients treated in North America in DECISION.
- The effect was statistically significantly in favour of lenvatinib (compared with placebo) for those with and without lung metastases in SELECT and the effect was statistically significantly in favour of sorafenib (compared with placebo) for those with lung metastases only and for those without lung metastases only in DECISION.
- The effect was statistically significantly in favour of lenvatinib (compared with placebo) and for sorafenib (compared with placebo) for patients with and without bone metastases in SELECT and DECISION.

It is recommended by the EMA[26] that before initiating treatment, physicians should carefully evaluate the prognosis in the individual patient, considering the maximum lesion size, symptoms related to the disease and the progression rate.

As reported in the appendices to the submission from Bayer HealthCare,[7] a post hoc analysis of investigator-assessed PFS by number of target lesions in DECISION found statistically significant improvements with sorafenib compared with placebo for patients with at least three lesions. For patients with fewer than three lesions, PFS was numerically improved with sorafenib compared with placebo. It is also reported that another

post hoc subgroup analysis of investigator-assessed PFS showed a treatment effect in favour of sorafenib compared with placebo for patients with maximum tumour size of ≥ 1.5 cm (HR 0.54, 95% CI 0.41 to 0.71). A numerically lower effect was reported for patients with a maximum tumour size of < 1.5 cm (HR 0.87, 95% CI 0.40 to 1.89).

Aside from the caveat surrounding the use of HRs to determine statistical significance as a result of PH assumption being violated, it is important to note that subgroup analyses are not powered to detect statistical significance. Therefore, when no statistically significant differences are reported, it could be that the numbers of patients in the subgroups were not large enough to detect a difference.

Extended open-label phases of SELECT and DECISION

In the extended open-label phase of SELECT, the starting daily dose of lenvatinib was originally 24 mg. This was later modified to 20 mg and then reverted to 24 mg. It is important to note that this phase of the trial only included 115 patients who crossed over from the placebo arm to lenvatinib and therefore does not present evidence from a randomised or controlled patient population. Furthermore, only placebo-treated patients who had confirmed disease progression (independent blinded review) during the randomisation phase and who met protocol-specified eligibility criteria were treated with lenvatinib. Consequently, it is noted in the EPAR[27] for lenvatinib that these patients had very advanced disease, because they had experienced two sequential, confirmed disease progressions: the first before randomisation at the time of study entry and the second during treatment with the study drug in the randomisation phase.

The extended open-label phase of DECISION differed to that of SELECT in that as well as including patients who crossed over from the placebo arm to receive sorafenib, it also included patients who remained on sorafenib. In total, 150 patients in the placebo arm crossed over to receive sorafenib at progression and of these, data from 137 patients were evaluable for efficacy. In addition, 55 patients randomised to the sorafenib arm continued on sorafenib treatment in the open-label extension phase, of which 46 patients were evaluable for efficacy. It is reported by Schlumberger *et al.*[122] and Paschke *et al.*[114] that patients evaluable for efficacy had poorer risk features at enrolment compared with patients who were not evaluable. Like the extended open-label phase of SELECT, evidence from this patient population does not comprise evidence from a randomised or controlled patient population.

Findings from the extended open-label phase of SELECT for only '. . . the more mature dataset of patients who started treatment at the 24mg lenvatinib dose' were reported in a conference abstract[118] describing the first data cut-off point (November 2013). Findings reported at the second data cut-off point (June 2014) were presented for patients who started treatment at the 20-mg dose of lenvatinib and for patients who started the 24-mg dose of lenvatinib in the EPAR for lenvatinib.[27] In the EPAR,[27] it is reported that patient characteristics, previous treatments, geographical allocation, on-study placebo exposure, lenvatinib exposure in the extended open-label phase and median follow-up times vary considerably for these two dose regimens. Thus, patients receiving the different dose regimens are considered by the EMA to represent different populations of patients.

In addition to conference abstracts,[114,122] the findings from the extended open-label phase of DECISION have been reported in the EPAR[46] for sorafenib. Safety data for the extended open-label phase of DECISION are reported in the submission from Bayer HealthCare.[7]

The efficacy and safety findings from the open-label phases of both trials are summarised in *Appendix 7*, *Tables 56* and *57*. OS data have not been reported. With the exception of median PFS for patients receiving sorafenib for a second time, which was 6.7 months, the efficacy findings for PFS from the extended phase of SELECT and DECISION were similar to the findings reported in the randomised phase of

the trials. The incidence of AEs for patients treated with lenvatinib and sorafenib in the open-label phases of the two trials tended to be slightly lower than reported during the double-blind phase.

In addition, Kappeler *et al.*[94] and Fassnacht *et al.*[83] have reported exploratory analyses of tumour growth rate in the randomised double-blind and extended open-label phases of DECISION. The authors found that the tumour growth rate (mean changes per month of sum of target lesion diameters) from baseline to nadir was –3.9% then +2.6% from nadir to progression for patients treated with sorafenib in the randomised phase; for those continuing with additional sorafenib in the open-label phase, from second baseline to progression the tumour growth rate was +1.7%. For patients randomised to the placebo arm, the tumour growth rate was +5.0% for all placebo patients and it was +6.1% for placebo patients subsequent to crossing over to receive sorafenib. Patients in the placebo arm who crossed over to sorafenib in the open-label phase then experienced a tumour growth rate pattern similar to that of patients who started on sorafenib in the randomised phase: –4.4% from second baseline to nadir and then +1.8% from nadir to progression.

Associations between tumour response, progression-free survival, overall survival, safety and health-related quality of life

Gianoukakis *et al.*[86] examined the association between ORR and PFS for patients treated with lenvatinib in SELECT. The analysis is based on the third data cut-off point (August 2015) using investigator-assessed ORR [60.2% (the proportion of patients who achieved an objective tumour response)] and investigator-assessed mean PFS (19.4 months). The authors found that the median PFS in patients who received lenvatinib and who demonstrated a tumour response was 33.1 months (95% CI 27.8 months to not estimable). In lenvatinib-treated patients who did not show tumour response, the median PFS was 7.9 months (95% CI 5.8 to 10.7 months). Robinson *et al.*[117] reported that an exploratory multivariate analysis found that percentage change in tumour size at the first assessment was a marginally statistically significant positive predictor for PFS ($p = 0.06$).

Using data from the first data cut-off point of SELECT, Newbold *et al.*[108] analysed PFS by patients who had responded to treatment with lenvatinib at the first tumour assessment (median time to response 1.9 months) and by those who responded later (median time to response 3.8 months). The authors found that there was no difference in PFS between patients who achieved objective response at the time of first tumour assessment compared with thereafter.

Haddad *et al.*[91] found from a multivariate analysis (first data cut-off point) that in SELECT, all-grade diarrhoea was statistically significantly associated with OS (median OS for lenvatinib-treated patients with diarrhoea was not reached and median OS for lenvatinib-treated patients without diarrhoea was 17.1 months). Choi *et al.*[79] reported that the results of a post hoc analysis showed that lenvatinib-treated patients with hypertension had higher median PFS than those without hypertension (18.8 vs. 12.9 months; $p = 0.009$). Haddad *et al.*[91] also reported results from multivariate analyses of associations between five other AEs (proteinuria, diarrhoea, fatigue/asthenia/malaise, rash and hand–foot syndrome) and PFS in SELECT. No statistically significant associations between any of the AEs and PFS were found.

Using data from DECISION, Kappeler *et al.*[95] carried out an exploratory analysis to explore the association between tumour growth rate and PFS and OS. It is reported that the data cut-off points used for PFS and OS were the first data cut-off point (August 2012) and third data cut-off point (July 2015), respectively. Values of early tumour growth rate were split into quartiles [by median times derived from Kaplan–Meier (K–M) curves and from modelling with a Weibull distribution] separately by treatment arm. Better prognosis for PFS and OS with sorafenib was associated with the second and third tumour growth rate quartiles.

No other analyses have been conducted for patients treated with either lenvatinib or sorafenib in SELECT or DECISION examining the relationships between any of the efficacy or safety outcomes and HRQoL. As reported earlier (see *Health-related quality-of-life findings*), it has been speculated that AEs did affect HRQoL based on data from FACT-G and EQ-5D questionnaires, but no formal analyses have been conducted in an attempt to correlate the findings.

Indirect comparison feasibility assessment

In the absence of direct clinical evidence comparing treatment with lenvatinib versus sorafenib, the AG considered whether or not it was appropriate to carry out an indirect comparison to obtain estimates of the relative efficacy and safety of these two treatments.

The first step was to determine whether or not SELECT and DECISION shared a common comparator. The comparator arm of both trials was placebo. From the limited information on the placebos reported by Eisai Ltd,[8] Bayer HealthCare[7] and in the published papers,[51,52] the AG considered that the comparator arms were likely to be similar and that a network could be constructed (*Figure 5*).

The second step was to check the comparability of the participant and trial characteristics between the two trials. As described in *Trial characteristics* and *Participant characteristics*, the AG has noted that there are several trial design and participant differences, both within and between SELECT and DECISION. These differences raised concerns about whether or not data from these trials should be included in the same network of evidence.

The final step undertaken by the AG was to examine the PFS K–M data from the placebo arms of SELECT and DECISION to determine the extent to which the risk profiles of the populations in these arms of the two trials were comparable. The AG concluded that the risks were not sufficiently comparable and that these two trials should, therefore, not be included in the same network of evidence.

The Assessment Group's detailed commentary on progression-free survival Kaplan–Meier data from the placebo arms

An indirect comparison implicitly assumes that the randomised patients are drawn from similar populations with reference to their risk profile for the time-to-event outcomes (PFS and OS). Because PFS is the primary outcome specified in both clinical trials, it is important that the equivalence of the placebo arms of the two trials can be confirmed by comparison of PFS outcomes: any significant discrepancy in progression risk would invalidate an indirect comparison between lenvatinib and sorafenib.

Figure 6 compares the K–M PFS trial results for the placebo arms of the two trials. After similar trends over the first 2 months, the curves separate markedly for more than a year before crossing over in the long term. Visual examination is sufficient to establish that these data are not amenable to either a simple HR adjustment or a time ratio adjustment.

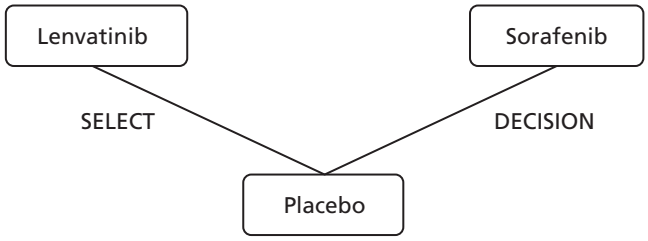

FIGURE 5 Indirect comparison network.

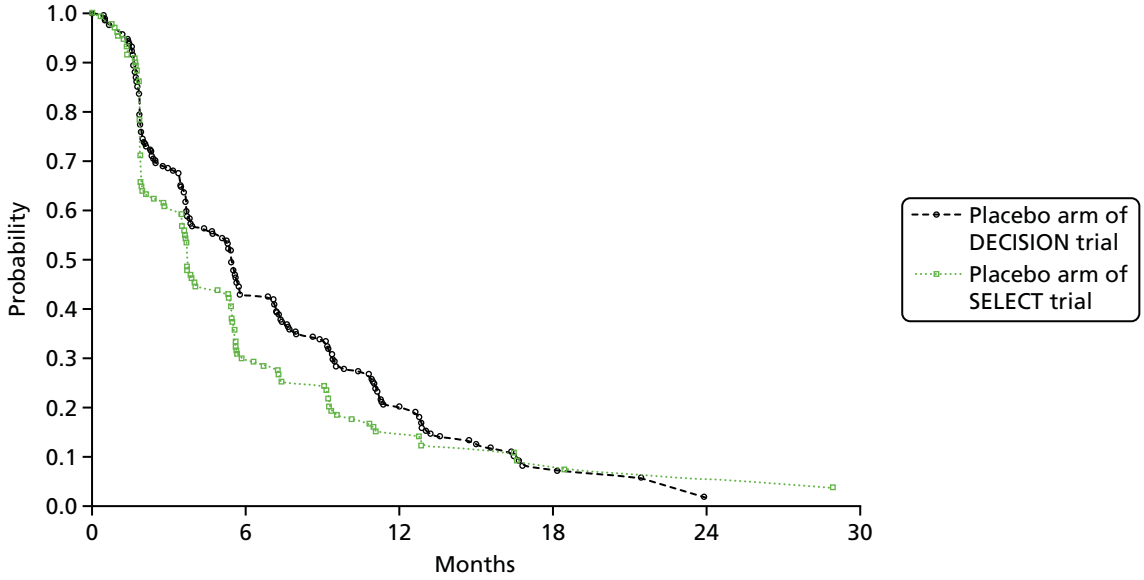

FIGURE 6 Comparison of PFS in the placebo arms of DECISION and SELECT. Reproduced with permission from Fleeman *et al.*[54] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Further exploration of these data trends through a plot of cumulative hazards in the two trial arms at common time points reveals a clear divergence from a simple linear (PH) relationship (*Figure 7*). The trial data indicate a higher initial risk of disease progression in SELECT in the first 10 months, followed by a sharp reversal in which the risk in the SELECT placebo arm reduces by > 50%.

The AG considers that the placebo arms of SELECT and DECISION exhibit unexpectedly inconsistent patterns of temporal change that are not compatible with the assumption that these are similar patient groups. Consequently, patients enrolled in the two trials cannot be considered to be derived from a common population and, therefore, conducting an indirect comparison to obtain estimates of relative efficacy for lenvatinib and sorafenib is not appropriate.

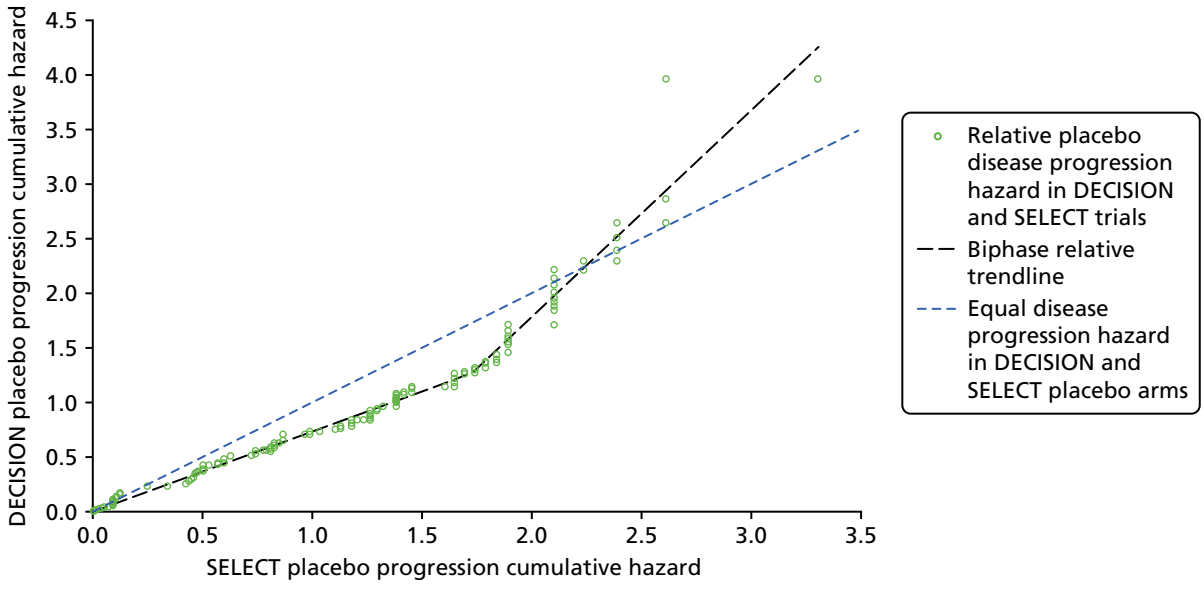

FIGURE 7 Comparison of PFS hazard trends in the placebo arms of DECISION and SELECT.

Differences in trial and participant characteristics in the placebo arms of the trials

As reported earlier (see *Trial characteristics* and *Participant characteristics*), a number of differences in trial and participant characteristics were observed between arms within trials and across trials. Given the apparent differences in the placebo arms of the two trials, as demonstrated by differing hazard trends, the AG highlights the following differences in characteristics between the two placebo arms:

- The SELECT trial permitted the enrolment of patients who had been previously treated with a VEGFR-targeted therapy (including sorafenib), whereas DECISION did not: 20.6% had received prior therapy in the placebo arm of SELECT compared with no patients in the placebo arm of DECISION.
- Palliative radiotherapy, which is commonly available as part of BSC in UK NHS clinical practice, was not permitted for patients in the placebo arm of SELECT.
- The proportion of patients who crossed over from the placebo arm of SELECT was 87.8% at the third data cut-off point, compared with 75.0% in DECISION.
- There were proportionately more males in the placebo arm of SELECT than in the placebo arm of DECISION (57.3% and 45.2%, respectively).
- A higher proportion of patients in the placebo arm of SELECT were classified as being white than were similarly classified in the placebo arm of DECISION (78.6% and 61.0%, respectively), whereas the opposite was the case for patients classified as Asian (18.1% and 24.8%, respectively).
- Proportionately fewer patients in the placebo arm of SELECT were from Europe (48.9%) and proportionately more were from North America (29.8%) compared with the patients in the placebo arm of DECISION (59.5% and 17.1%, respectively).
- A greater proportion of patients in the placebo arm of SELECT had an ECOG PS of ≥ 1 (48.1%) than in the placebo arm of DECISION (38.6%).
- A greater proportion of placebo patients had FTC and poorly differentiated thyroid cancer in the placebo arm of SELECT (16.8% and 14.5%, respectively) than in the placebo arm of DECISION (9.0% and 7.6%, respectively).
- The time from diagnosis to randomisation was greater in the placebo arm of SELECT (73.9 months) than in the placebo arm of DECISION (66.9 months).
- A greater proportion of patients in the placebo arm of SELECT had lung, bone and liver metastases (94.7%, 36.6% and 21.4%, respectively) than in DECISION (86.2%, 26.7% and 14.3%, respectively).

Proportional hazards assumption

As discussed in *Consideration of proportional hazards assumption*, the AG concluded that the PH assumption was not valid for PFS, unadjusted OS or adjusted OS in SELECT or for PFS or adjusted OS in DECISION. The violation of the PH assumption, for all but unadjusted OS in DECISION, means that the network of evidence is compromised for all outcomes.

Assessment Group summary statement

The AG considers that is not appropriate to conduct an indirect comparison to obtain HRs for lenvatinib versus sorafenib for the outcomes of PFS, unadjusted OS and adjusted OS. This is because the risk profiles of the patients in the placebo arms of the trials are not comparable and any indirect comparison would produce results that could not be considered to be robust. This also precluded indirect comparison for subgroups of patients according to previous treatment with TKIs.

As described in *Chapter 3*, *Methods of analysis/synthesis*, in addition to trial characteristics, participant characteristics and outcome data, the AG stated that it would consider the quality of the included trials when conducting its feasibility assessment. The results of the AG's risk-of-bias assessment are reported in *Comparison of assessments of risk of bias*. However, given the issues already highlighted, the quality of the trials was not a factor in the AG's decision to not conduct an indirect comparison.

Systematic review evidence

The AG included 13 systematic reviews[5–8,33,57,61,93,97,104,127,138,141] in its review; these reviews included the evidence submissions reporting systematic reviews and indirect comparisons for this MTA from Eisai Ltd[8] and Bayer HealthCare,[7] and also the evidence reported in a paper by Tremblay *et al.*[57] Although Tremblay *et al.*[57] did not report the conduct of a systematic review, this paper was included as it did report results from an indirect comparison and a matching-adjusted indirect comparison (MAIC) using data from SELECT and DECISION.

A summary of the characteristics of the included systematic reviews is presented in *Appendix 5*, *Table 49*. Most of the evidence was derived from observational studies of treatment with sorafenib. However, four of the reviews,[7,8,57,97] including the submissions from Eisai Ltd[8] and Bayer HealthCare,[7] included evidence from SELECT and DECISION and results from indirect comparisons, including MAICs.

The AG's assessment of the quality of the included reviews is presented in *Appendix 5*, *Table 50*. Overall, the AG considered that the quality of nine[5–8,61,97,104,127,138] of the identified systematic reviews was good. However, only 4[5–8] of the 13 reviews included a quality assessment of the included primary studies. Four[33,57,93,141] of the reviews were considered to be of poorer quality than the rest. Of these, only one[33] reported the use of an adequate search strategy. In addition, methods of cross-checking during either the study selection process or the data extraction process were not reported by the authors of three reviews.[33,57,93] No quality assessment of the primary studies was reported in any of these four reviews.[33,57,93,141]

The conclusions reached by the authors of the systematic reviews are presented in *Appendix 5*, *Table 51*. The earliest of the reviews was carried out by Anderson *et al.*[61] and was published in 2013. The authors concluded that certain treatments, notably TKIs, showed promise in Phase II trials. Gruber and Colevas[33] concluded that the most likely outcome of treatment with a TKI was stable disease. McFarland and Misiukiewicz[104] concluded that sorafenib slowed the progression of disease in the majority of cases. For treating thyroid cancer, Ye *et al.*[141] reported that the clinical effects of sorafenib and lenvatinib outweigh the toxicities [relative risk (RR) 1.27, 95% CI 1.05 to 1.53] and deaths (RR 15.24, 95% CI 6.99 to 33.21). Ye *et al.*[141] concluded that lenvatinib and sorafenib were more useful for thyroid cancer than for RR-DTC, based on the results of the subgroup analyses that were conducted. However, the AG considers that all of the studies that included patients with DTC also included patients with RR-DTC and so the validity of this subgroup analysis and the conclusions reached based on these subgroup analyses are questionable.

Jean *et al.*[93] found AEs reported for sorafenib for treating RR-DTC to be higher than for AEs reported for treating renal cell carcinoma (RCC) or hepatocellular carcinoma (HCC). In two reviews[127,138] ORR data and AE data were pooled for sorafenib from seven observational studies[59,78,88,101,126,147,148] (five prospective and two retrospective). In the review by Shen *et al.*,[127] all of the studies[59,78,88,101,126,147,148] included patients with RR-DTC, whereas the review by Thomas *et al.*[138] included five prospective observational studies of RR-DTC,[59,88,101,126,147] a retrospective study of RR-DTC[149] and a Phase II study[150] of patients with medullary thyroid cancer. Although the incidences of hand–foot syndrome (≥ 73%), diarrhoea (≥ 68%) and weight loss (≥ 50%) included in both meta-analyses were broadly similar to the incidence of the same AEs in DECISION, it was noticeable that the incidences of rash (≥ 66%) and fatigue (≥ 60%) were higher than reported in DECISION. Similarly, the pooled ORR (20.9% to 22%) from the two reviews[127,138] was higher than the ORR reported in DECISION. The pooled median PFS (17.9 months) from the review by Thomas *et al.*[138] was also higher than median PFS reported in DECISION, but the pooled analysis for PFS also included patients with medullary thyroid cancer. The key results from these three reviews[93,127,138] are summarised in *Appendix 5*, *Table 52*.

In addition, Shen *et al.*[127] noted that rare but severe AEs were observed mainly due to intracranial haemorrhage, cardiac arrest, angiooedema, small cell lung cancer, carcinoma of the tongue, and grade 5 event of sudden death. Because of the limited data, the authors did not pool these high-grade AEs. Thomas *et al.*[138] also reported that bleeding at any site occurred in 13.6% of patients, 3.8% of patients reported acute myocardial infarctions and 2.2% experienced congestive heart failure. Severe hypocalcaemia (grade ≥ 3)

occurred in 2.5% of patients and 8.7% of patients developed cutaneous squamous cell carcinoma. However, it should be cautioned that in the meta-analyses conducted by Shen *et al.*[127] and Thomas *et al.*,[138] the authors did not investigate the heterogeneity of the studies included in the meta-analyses.

For RR-DTC, all of the indirect comparison results (including results from MAICs[7,57]) showed that lenvatinib was statistically significantly superior to sorafenib in terms of PFS but not OS.[6–8,57,97] Kawalec *et al.*[97] also reported lenvatinib to result in statistically significantly fewer cases of alopecia but statistically significantly more cases of hypertension and treatment-related SAEs, when compared with sorafenib. Bayer HealthCare[7] reported sorafenib to result in fewer grade ≥ 3 AEs, SAEs and withdrawals owing to AEs when compared with lenvatinib. However, caveats about the generalisability of the results of the indirect comparisons have been raised,[6] and Kawalec *et al.*[97] stated that indirect comparison results should be interpreted with caution because of differences in trial characteristics. Furthermore, during the current appraisal, Bayer HealthCare confirmed that it considered that the data from its indirect treatment comparison (ITCs)[7] did not enable a robust comparison of sorafenib and lenvatinib given important differences between SELECT and DECISION.[151] Of the indirect comparisons conducted, only the indirect comparison by Kawalec *et al.*[97] was not sponsored by Eisai Ltd or Bayer HealthCare. A summary of the findings from the indirect comparisons is presented in *Appendix 5*, *Tables 53–55*.

Evidence from prospective observational studies

The AG included nine prospective observational studies in its review.[59,77,78,81,88,101,103,126,135] Five of these studies[59,78,88,101,126] were included in the meta-analyses conducted by Shen *et al.*[127] and by Thomas *et al.*[138] Seven of the studies were included in the EPARs[26,27] for lenvatinib[77,135] and sorafenib.[59,78,88,101,126] The study and participant characteristics and efficacy and safety findings are summarised in *Appendix 8*, *Tables 58–68*.

All studies included patients whose disease was described as being radioactive iodine-refractory[59,77,78,101,126,135] or resistant to radioactive iodine,[81,88] or who may have received multiple treatments of radioactive iodine.[103] Two studies[77,135] investigated the efficacy and safety of lenvatinib, six studies[59,78,88,101,103,126] assessed the efficacy and safety of sorafenib and one study[81] considered the efficacy of sorafenib. Some patients included in four of the studies[59,88,101,135] had anaplastic or medullary carcinoma. Safety data from these four studies[59,88,101,135] are, therefore, not reported for RR-DTC only. However, all nine studies[59,77,78,81,88,101,103,126,135] reported efficacy findings for patients with RR-DTC only and all efficacy data reported in this section related to patients with RR-DTC only.

The E7080-G000-201 study (hereafter referred to as Study 201[77]) of lenvatinib was conducted in the UK, France, Italy, Poland, the USA and Australia. The E7080-J081-208 study of lenvatinib (hereafter referred to as Study 208[135]) was conducted in Japan. Studies of sorafenib were carried out in the UK,[59] the Netherlands,[126] Italy,[103] Greece,[81] the USA[101] and China.[78] The earliest study was conducted between 2004 and 2005,[101] and the most recent study was conducted between 2012 and 2015.[135] The length of study follow-up varied from a minimum of 3 months[78] to a median of 51.6 months.[27]

The number of patients included in the studies varied from 9[78] to 58.[77] In total, 109 patients were treated with lenvatinib, of whom 83 had RR-DTC; 213 patients were treated with sorafenib, of whom 186 had RR-DTC. In most studies, the majority of patients with RR-DTC had a histology of PTC,[59,77,78,88,101,126] the exception being the study by Marotta *et al.*[103] in which the ratio of patients with FTC to patients with PTC was 2 : 1. The average age of participants ranged from 55 years[59] to 64 years.[101] Four studies[59,77,88,101] included a majority of males and three studies[81,103,126] had a majority of females. Two studies[78,135] did not report information on sex. The authors of only two studies[77,101] reported information on race and these included a majority of white participants. Only two studies that reported ECOG status included patients with an ECOG PS of ≥ 2 (6.9%[77] and 35.3%[103]). The same two studies were the only studies to explicitly state that patients could have received a prior TKI (11.8%[103] to 29.3%[77]). There was scant and inconsistent reporting of the sites of metastases.

Median OS was reported in five studies.[77,88,101,126,135] Median OS ranged from 31.8 months[135] to 32.3 months[77] for lenvatinib and from 23 months[101] to 34.5 months[126] for sorafenib. Median PFS was reported in six studies[77,88,101,103,126,135] and ranged from 12.6 months[77] to 25.8 months[135] for lenvatinib and from 12 months[103] to 22.1 months for sorafenib[88] (this last finding was reported in a subsequent conference abstract[137]). Chen *et al.*[78] (sorafenib) reported mean PFS (9.7 months). The ORRs ranged from 50.0%[77] to 68.0%[135] for patients treated with lenvatinib, and from 15% (histology of PTC)[101] to 38.3%[88] for those treated with sorafenib (this latter finding was reported in a subsequent conference abstract[137]). Median time to response and median duration of response were only reported in two studies.[77,126] For lenvatinib,[77] median time to response was 3.6 months and, for sorafenib,[126] all responses were reported to have happened within 6 months. The median duration of response was 12.7 months for lenvatinib[77] and 29.6 months for sorafenib.[126]

Key AEs are summarised in *Appendix 8*, *Tables 61–66*. Two studies[88,101] (sorafenib) only reported treatment-related AEs. Two of the sorafenib studies,[78,81] presented only as abstracts, reported very little information about AEs.

Incidences of the same types of AEs varied across the studies: for lenvatinib, hypertension and proteinuria were very commonly reported; for sorafenib, hand–foot syndrome, rash and alopecia were common; and diarrhoea and fatigue were common with both drugs. Data on SAEs were available only from Study 201[77] (lenvatinib). Information on fatal AEs were reported only in two studies[77,135] of lenvatinib and in one study[101] of sorafenib. For patients treated with lenvatinib, 48% reported a SAE[77] and up to 8%[135] died from an AE. Only one death from AEs has been reported in one of the studies of sorafenib;[101] it is unclear if the lack of reporting of fatal AEs in the other sorafenib studies[59,78,81,88,103,126] means that there were no deaths from AEs in these studies. None of the deaths from AEs in any of the three studies[77,101,135] reporting fatal AEs were described as being treatment related.

Ongoing studies and studies for which there are no results

The AG identified four ongoing studies,[152–155] as summarised in *Appendix 9* (see *Table 69*). None of the study results has been published or reported as a conference abstract. Only the two studies of lenvatinib[154,155] are RCTs: E7080-G000-211 (Study 211)[154] is a Phase II postauthorisation study that includes a randomised controlled phase, comparing two different starting doses of lenvatinib (24 vs. 18 mg) with placebo; E7080-C086-308 (Study 308)[155] is a Phase III RCT being conducted in China comparing lenvatinib at its licensed dose of 24 mg with placebo. Eisai Ltd sponsors both of these trials. The other two studies are prospective observational Phase II studies of sorafenib:[152,153] a pilot study sponsored by the Royal Marsden NHS Foundation Trust[152] and a postauthorisation study sponsored by Bayer HealthCare.[153]

In addition, although not strictly meeting the inclusion criteria for the current MTA, the AG is aware of an ongoing global prospective non-interventional study [Radioactive Iodine reFractory asymptomatic patients (RIFTOS), NCT02303444][156] of asymptomatic patients with RR-DTC treated with any type of MKI. The primary objective is to compare the time to symptomatic progression from study entry. Bayer HealthCare sponsors this study. The planned enrolment is approximately 700 patients and the expected study end date is 1 July 2020.

Discussion of clinical effectiveness: interpretation of results

The AG's assessment of lenvatinib and sorafenib for the treatment of patients with RR-DTC focused on evidence from two RCTs: SELECT (lenvatinib vs. placebo) and DECISION (sorafenib vs. placebo). Supporting evidence was derived from 13 systematic reviews[5–8,33,57,61,93,97,104,127,138,141] (including two systematic reviews described in the submissions from Eisai Ltd[8] and Bayer HealthCare[7]) and nine prospective observational studies.[59,77,78,81,88,101,103,126,135]

Clinical efficacy

Summary and interpretation of evidence: lenvatinib versus sorafenib

The primary objective of the AG's systematic review was to compare the clinical effectiveness of lenvatinib with that of sorafenib. Results from the AG's literature search revealed that there have been no head-to-head trials comparing the effectiveness of treatment with lenvatinib with the effectiveness of treatment with sorafenib. However, five studies[6–8,57,97] have reported results from indirect comparisons and/or MAICs. Results from all of these analyses show that, compared with sorafenib, treatment with lenvatinib improves PFS but not OS.

The AG explored whether or not it was appropriate to conduct an indirect comparison. Although it was possible to construct a network, the AG identified issues that raised concerns about whether or not evidence from SELECT and DECISION could be included in the same network. First, there were differences between trial characteristics (prior treatment with TKIs, concurrent use of palliative radiotherapy and differences in subsequent treatment received on disease progression). Second, there were differences in participant characteristics (sex, race, geographic region, ECOG PS, time from diagnosis, histology and site of metastases) both within and between the trials. Third, the analysis of the PFS K–M data from the placebo arms of SELECT and DECISION showed that the risk profiles of the two trial populations were not comparable. The reasons for the differences in risk are currently unknown. Fourth, the AG considered that, for the majority of patient survival hazards assessed in the two trials, PHs were violated, the exception being unadjusted OS in DECISION.

The AG is unable to conclude whether or not treatment with lenvatinib is more effective than treatment with sorafenib for patients with RR-DTC. The AG considers that the results from the four published indirect comparisons[7,8,57,97] should be interpreted with caution. This warning also extends to the results from the MAICs.[7,57] It is unknown whether or not the MAIC adjustments would fully account for all of the differences in the trial populations because the AG was unable to compare the adjusted risk profiles of patients included in the MAIC.

The AG highlights that Kawalec *et al.*[97] stated that their indirect comparison results should be interpreted with caution because of differences in the characteristics of the included trials. In addition, the EMA,[27] Scottish Medicines Consortium (SMC)[38] and Canadian Agency for Drugs and Technologies in Health (CADTH)[6] all highlighted that differences in populations might have contributed to differences in results observed between the two trials. The SMC[38] also highlighted that the validity of the results from the MAIC submitted by Eisai Ltd may be limited by weaknesses including heterogeneity across the studies in inclusion criteria, assessment of disease progression and analysis of PFS. The CADTH[6] highlighted that the MAIC approach does not have the ability to control for the potential for unobserved or unrecorded differences between trials such as differences in standards of care or baseline characteristics. Furthermore, during the current appraisal, Bayer HealthCare confirmed that it considered that the data from its ITCs[7] did not enable a robust comparison of sorafenib and lenvatinib given important differences between SELECT and DECISION (Bayer HealthCare response to AG report to the NICE Appraisal Committee, 6 September 2017).[157]

Summary and interpretation of evidence: lenvatinib and sorafenib versus best supportive care

The secondary objective of the AG's systematic review was to compare treatment with lenvatinib and sorafenib with BSC. The AG has assumed that, in both trials, treatment with lenvatinib plus BSC or sorafenib plus BSC is compared with placebo plus BSC. The unadjusted OS results from SELECT and DECISION demonstrated that there was no statistically significant difference in OS between treatment with lenvatinib and treatment with sorafenib versus placebo. After adjusting OS data for treatment crossover using RPSFTM, there was a statistically significant improvement in OS from treatment with lenvatinib compared with placebo; however, the difference in effect of sorafenib versus placebo was not statistically significant. The AG highlights that the unadjusted median OS estimates for patients treated with lenvatinib

and sorafenib in SELECT and DECISION are higher than those reported for patients treated with lenvatinib and sorafenib in prospective observational studies.

For PFS and ORR, the results from SELECT and DECISION demonstrated that treatment with both lenvatinib and sorafenib were statistically significantly better than treatment with placebo for patients with RR-DTC. For all of the prespecified subgroups, the results from SELECT and DECISION favoured treatment with the intervention (lenvatinib or sorafenib) when compared with placebo. Median PFS and ORR for patients treated with lenvatinib in SELECT were higher than the prospective observational results from Study 201[77] and lower than the results from Study 208.[135] In contrast, median PFS and ORR results reported for patients treated with sorafenib (DECISION) were lower than findings from any of the prospective observational studies or the two meta-analyses.[127,138]

Patients in DECISION were permitted to receive concomitant palliative radiotherapy, a common component of BSC in NHS clinical practice, whereas patients in SELECT were not; full details of the BSC provided in the two trials are not available. Whether or not patients in the trials received BSC similar to that provided by the NHS is unknown and this raises uncertainty about whether or not the trial results are generalisable to NHS patients. If the BSC delivered in the two trials is not comparable, then using the placebo arms to connect the two trials in an indirect comparison becomes even more challenging. However, as the rates of palliative radiotherapy administered to patients in DECISION are low (10.6% of patients treated with sorafenib and 21.4% of patients treated with placebo), then perhaps this issue is not important.

There are two important issues to consider when interpreting the RCT evidence. First, a caveat to the use of the RPSFTM-adjusted OS results from both trials is that the method requires the assumption that postprogression anti-cancer treatments, other than those permitted by treatment crossover, represent routine clinical practice. For patients with RR-DTC, there is currently no standard of care for patients with progressive disease. Therefore, it is unknown whether or not the poststudy anti-cancer treatments administered to patients in SELECT and DECISION reflect the treatments that would be offered to patients in the NHS. Second, the AG's examination of the PH assumption for OS (unadjusted and adjusted) and PFS in SELECT and DECISION showed that the PH assumption does not hold for any of these outcomes other than unadjusted OS in DECISION. This means that the majority of the HRs reported in the company submissions should be interpreted with caution. However, clinical advice to the AG is that the PFS results for the overall populations of SELECT and DECISION are clinically meaningful.

Safety

Summary and interpretation of evidence: lenvatinib versus sorafenib

The AG did not conduct its own indirect comparison to facilitate a comparison of the effect of treatment with lenvatinib with the effect of treatment with sorafenib for AEs. However, two other reviews[7,97] reported results from indirect comparisons of AEs. Kawalec *et al.*[97] reported that treatment with lenvatinib resulted in statistically significantly less alopecia but statistically significantly more hypertension and treatment-related SAEs than sorafenib. Bayer HealthCare[7] reported sorafenib to result in fewer grade ≥ 3 AEs, SAEs and withdrawals owing to AEs when compared with lenvatinib.

Summary and interpretation of evidence: lenvatinib and sorafenib versus best supportive care

When compared with placebo, treatment with both lenvatinib and sorafenib resulted in increased AEs. However, although diarrhoea was experienced by just over two-thirds of patients treated with both drugs in SELECT and DECISION, there were some notable differences in the safety profiles. Hypertension and decreased appetite were reported by over half of patients in SELECT, whereas the most common AEs reported by half or more of patients in DECISION were hand–foot syndrome, alopecia and rash. Grade ≥ 3 hypertension was very common in patients treated with lenvatinib (> 40%), and grade ≥ 3 hand–foot syndrome was very common in patients treated with sorafenib (> 20%). Hypertension was also reported to be one of the most common SAEs in SELECT (3.4%). Data on the median time to onset of AEs[91,139] from SELECT and DECISION suggest that AEs typically occur early, with a decrease in incidence, prevalence and

severity over time. In DECISION, exceptions were diarrhoea that increased in prevalence over the first six cycles and weight loss that increased in severity (from grade 1 to grade 2) over the first nine cycles.

Overall, the safety findings from the RCTs were consistent with the findings from prospective observational studies of lenvatinib[77,135] and sorafenib,[59,78,81,88,101,126] although it is noticeable that the incidence of some AEs varied quite widely in observational studies for patients treated with sorafenib. However, meta-analyses[127,138] of data from observational studies for hand–foot syndrome and diarrhoea reported incidences of all-grade and grade ≥ 3 AEs to be similar to those reported in DECISION. It has, however, been found in a systematic review by Jean *et al.*[93] that the incidence of common all-grade AEs tends to be higher for patients with RR-DTC than for patients with RCC or HCC and also for some patients with grade ≥ 3 hand–foot syndrome and rash.

After diarrhoea, hypertension was the most common reason for dose modifications, as well as being the most common reason (alongside asthenia) for discontinuations in SELECT. In DECISION, the most common reason for dose modifications and discontinuations was hand–foot syndrome. Dose reductions were frequent (> 60%) for patients treated with both lenvatinib and sorafenib. Life-threatening AEs from treatment with lenvatinib and sorafenib were rare. The AG considers that the AEs associated with treatment with lenvatinib and sorafenib can be managed with usual medical care and dose modifications, including treatment withdrawal. Clear guidance for managing AEs is set out in the SmPCs for lenvatinib[45] and sorafenib.[46]

Health-related quality-of-life findings

The HRQoL data were not collected as part of SELECT, and HRQoL data from the 30 patients who participated in the open-label extension phase of SELECT are not yet available. This is disappointing given that the investigators in the earlier DECISION had measured and reported HRQoL outcomes and highlighted that HRQoL may be negatively impacted by treatment with TKIs.[7,120] AE rates were high in SELECT and it would have been informative if HRQoL data had been collected. HRQoL research is much needed as HRQoL is one of the most important outcomes to consider, both from the perspective of patients and for assessing comparative cost-effectiveness.

The HRQoL data collected during DECISION demonstrated that the FACT-G scores were higher for patients in the placebo arm than for patients in the sorafenib arm, indicating a higher HRQoL for patients receiving placebo. The negative impact of treatment with sorafenib on HRQoL may be linked to the high rates of AEs.[7,120] Indeed, it has been noted by Bayer HealthCare[7] that in response to the question on the FACT-G questionnaire 'I am bothered by side effects', the proportion of patients in the sorafenib arm who replied 'quite a bit' or 'very much' increased from 1.5% in cycle 1 to 29.6% in cycle 2 but then gradually diminished over time.

There are, however, limitations to the results from the HRQoL analyses. Although the overall questionnaire completion rate during DECISION was reported to be 96%,[120] the number of patients eligible to complete the questionnaires diminished with every cycle because only those who had not experienced progression were asked to complete the questionnaire. This also means that there are no HRQoL data available from patients whose disease has progressed. It is also unknown whether or not there is a direct correlation between HRQoL and AEs and how the different types of AEs experienced by patients treated with lenvatinib (e.g. hypertension) and sorafenib (e.g. hand–foot syndrome) affect HRQoL. Finally, to what extent a patient's HRQoL is affected by their symptom status (symptomatic vs. asymptomatic) is unknown.

Generalisability of findings

The AG considers that the generalisability of the findings from SELECT and DECISION to NHS clinical practice is questionable. This concern is driven by the fact that clinical advice to the AG is that in clinical practice there are concerns about the toxicity of TKI therapy in patients and effects on the quality of life of patients with asymptomatic disease and so treatment is more commonly given when symptomatic or clinically significant progressive disease develops. Hence, BSC is a common treatment option for this group. The authors of two of the meta-analyses of sorafenib[127,138] concluded that the high incidence of

AEs associated with sorafenib may affect the quality of patients' lives and most patients with metastatic disease do not require systemic therapy. This view is supported by several clinical guidelines[4,24,25] as patients experiencing RR-DTC symptoms and/or those with rapidly progressing disease are considered to be in greatest need of systemic treatment.[31] In addition, the EMA concluded that maximum lesion size, symptoms related to the disease and progression rate should be carefully considered for each individual patient before initiating treatment.[26]

Although all of the patients in SELECT and DECISION had RR-DTC, it is unclear how many had symptomatic and/or rapidly progressing disease; however, it is reported in the EPAR[26] for sorafenib that results from a post hoc subgroup analysis of data from DECISION suggest that 20% of patients were likely to be symptomatic. Clinical advice to the AG is that this is probably typical of the proportion seen in clinical practice. It is unclear how many patients in SELECT were symptomatic and/or had progressive disease.

The post hoc retrospective analysis of data from patients participating in DECISION[113,119] categorised patients as having symptomatic disease if they had symptoms/findings that were consistent with RR-DTC reported in the medical history or pre-treatment AE data set at baseline. Clinical advice to the AG is that there are no generally agreed definitions of 'symptomatic' or 'rapidly progressive disease' and that, in clinical practice, the definition of a patient's disease status depends on individual patient characteristics.

Results from the post hoc analysis show that median PFS was similar for all patients treated with sorafenib, irrespective of whether or not they were symptomatic or asymptomatic (10.7 months and 10.8 months, respectively, compared with 10.8 months for all patients in the sorafenib arm of the trial).[7] However, for patients in the placebo arm, median PFS was much lower for symptomatic patients (3.6 months) than for asymptomatic patients (7.2 months), and it was also lower than for all patients in the placebo arm of the trial (5.8 months).

No analyses have been undertaken to compare the effectiveness of treatment with lenvatinib for symptomatic patients with that for asymptomatic patients. In the absence of such analyses, no assumptions can be made about relative effectiveness. However, clinical advice to the AG is that, like sorafenib, only patients with symptomatic and/or progressive disease are likely to be treated with lenvatinib in the NHS.

The most recent published guidelines for treating RR-DTC, by the NCCN,[25] recommend lenvatinib or sorafenib as the treatment of choice for patients with progressive and/or symptomatic disease. However, the choice between lenvatinib and sorafenib should be based on the individual patient, taking into account the likelihood of response and comorbidities.[25]

There are further important caveats regarding the generalisability of the findings from SELECT and DECISION to NHS clinical practice.

The first caveat is that, although most patients participating in the trials had a diagnosis of PTC, as would be expected in clinical practice, there were proportionately more patients with other types of DTC than would be expected in NHS clinical practice. Patients with these other types of DTC are reported to have a worse prognosis than patients with PTC.[15] However, subgroup and exploratory analyses of SELECT data showed that for unadjusted OS, there was a statistically significant OS gain for patients with FTC treated with lenvatinib compared with those treated with placebo,[82] and that histology (favouring FTC vs. PTC) was statistically significantly associated with increased OS.[91] These exploratory results warrant further investigation.

The second caveat relates to the age of patients. Thyroid cancer incidence is strongly related to age, with the highest incidence rates being in older males (aged > 60 years) and the highest incidence rates in females being in younger and middle-aged women (aged 40–60 years).[1] The median age of patients was 61 years in the lenvatinib arm and 64 years in the placebo arm of SELECT and 63 years in both arms of DECISION, and approximately half of the patients in both trials were male. Given that the median time from diagnosis in the trials varied from between 5.5 and 6 years, it appears that, in general, patients were

older than may be seen in clinical practice. Moreover, the prognosis of patients tends to differ for patients aged < 45 years and for those aged ≥ 45 years, as reflected in the staging criteria used for DTC.[4] Detailed data on the age range of included patients were not reported for either trial.

Other issues of relevance to clinical practice

The relative importance of ORR also warrants some discussion, particularly given the marked reported differences in effect between treatment with lenvatinib and sorafenib indicated by results from SELECT and DECISION and the prospective observational studies.[59,77,78,81,88,101,103,126,135] Although studies of lenvatinib[51,77,135] suggest that at least half of all patients achieve a response, meta-analyses of data from observational studies of sorafenib[127,138] suggest that no more than 22% of patients receiving this treatment respond. This finding reflects the finding from a systematic review of TKIs[33] that shows that the most likely outcome of treatment with a TKI is stable disease. Indeed, in DECISION, 42% of patients in the sorafenib arm had stable disease for ≥ 6 months (and 12.2% had an objective tumour response) compared with 33% in the placebo arm (and 0.5% had an objective tumour response). However, given that lenvatinib and sorafenib are likely to be preferred treatment options for patients with clinically significant progressive disease, reducing the rate of disease progression may be a more relevant outcome. The AG notes that in the submission from Bayer HealthCare,[7] it is reported that most patients (77%) in the sorafenib arm of DECISION experienced target lesion tumour shrinkage, compared with 28% of patients in the placebo arm. The authors of a systematic review of sorafenib[104] for treating RR-DTC concluded that, although the data in the review came primarily from non-randomised Phase II trials (but also included DECISION), the results suggest that treatment with sorafenib slows the progression of disease in the majority of cases.

The findings from the extended open-label phases of SELECT and DECISION should also be considered. These findings show that the median PFS and ORR outcome results for patients previously randomised to the placebo arms but who crossed over to receive lenvatinib or sorafenib at the licensed doses were similar to the median PFS and ORR reported for patients treated with lenvatinib and sorafenib in the double-blind phases of the trials. Given that patients in the placebo arm received no active systemic therapies during the double-blinded phase, these results appear to support the view that patients with progressive disease do not need to be treated immediately and can be treated when showing symptoms and/or rapidly progressing. However, the AG cautions that data on symptoms and/or whether or not patients were rapidly progressing are lacking, although patients were progressing to the extent that, on the basis of RECIST (Response Evaluation Criteria in Solid Tumours) criteria, they were considered to have progressive disease. The AG also cautions that no OS data were available for these specific cohorts of patients.

The results from the open-label phase of SELECT, which included patients who crossed over from placebo to receive treatment with two different doses of lenvatinib, suggest that PFS may be improved for those starting at the 20-mg dose (median PFS not reached) as opposed to the licensed dose of 24 mg (median PFS of 17.5 months). However, the numbers of patients in each group, particularly in the 20-mg dose cohort, were small, and definitive conclusions could not be reached. Study 211,[154] an ongoing Phase II RCT, compares two different starting doses of lenvatinib (24 vs. 18 mg) with placebo. This trial is expected to end in October 2020.

Although patients treated with lenvatinib in SELECT were not permitted to receive additional lenvatinib in the extended open-label phase of that trial, around one-quarter of patients had received treatment with a VEGFR-targeted therapy, including sorafenib, prior to enrolment. SELECT subgroup PFS and ORR findings suggest that patients benefited from treatment with lenvatinib, regardless of whether or not they had received prior treatment with a VEGFR-targeted therapy. This result suggests that lenvatinib could be used as a first- or second-line treatment for patients with RR-DTC. Further research is required to identify the effect on OS of treating patients with lenvatinib followed by sorafenib. Furthermore, it has also been reported that SAEs were more common in the lenvatinib arm among patients who had received a prior VEGFR-targeted treatment (60.6%) than among those who had not (50.8%).[105,106]

Some patients in DECISION who had experienced disease progression while receiving sorafenib were also eligible to receive sorafenib for a second time in the extended open-label phase of DECISION. Clinical advice to the AG was that, in NHS practice, patients could be prescribed sorafenib post progression as there is a view that continued treatment with sorafenib will slow the progression of disease. This expectation is supported, to some extent, by exploratory post hoc findings.[83,94] These findings suggest that despite evidence of tumour growth or prior RECIST progression, treatment with sorafenib continued to slow tumour growth for patients who had also been treated with sorafenib during the randomised phase, when compared with tumour growth for patients treated with placebo during the randomised phase.[83,94] However, as concluded by authors of other abstracts[114,122] reporting results from the open-label extension phase of DECISION, the effect of continued treatment with sorafenib after progression needs to be explored further.

Finally, there are no data for patients treated with sorafenib followed by lenvatinib. Further research is needed to identify the effect on OS and other efficacy and safety outcomes of treating patients with lenvatinib followed by sorafenib, and sorafenib followed by lenvatinib.

Chapter 5 Assessment of cost-effectiveness

The AG conducted a systematic review of the economic literature to identify the existing evidence assessing the cost-effectiveness of treatment with lenvatinib and sorafenib (vs. each other and vs. BSC) for people with progressive, locally advanced or metastatic RR-DTC. The review focused on the decision problem outlined in the final scope issued by NICE.[53] The economic evaluations presented in the submissions by Eisai Ltd[8] and Bayer HealthCare[7] are discussed and critiqued separately in *Summary of the key features of the companies' economic models*.

Search strategy

The AG identified cost-effectiveness studies by searching EMBASE, MEDLINE, the NHS Economic Evaluation Database via The Cochrane Library and EconLit from 1999 onwards. The starting date for all of the searches was 1999 and all databases were searched on 10 January 2017. Based on the fact that the FDA approved sorafenib for its first indication in 2005, and lenvatinib in 2015, the AG considered that this date span would allow all relevant economic evidence to be identified. The reference lists of included publications, in addition to the NICE, SMC and CADTH websites, were hand-searched. The results of the searches were entered into an EndNote X7.4 library and de-duplicated.

Study selection and inclusion criteria

Publications were selected for inclusion in the review based on their relevance to the decision problem and the specific economic criteria presented in *Table 12*. In addition to costs, quality-adjusted life-years (QALYs), cost–benefit and cost-effectiveness outcomes, such as cost per PFS year, were also extracted from relevant publications.

Two reviewers (RH and NF) independently screened the titles and abstracts of all publications identified by the searches. The same two reviewers then independently retrieved and assessed (for inclusion) the full texts of the publications that had been identified as being potentially relevant to the review. Disagreements about inclusion in the review were resolved through discussion and, in all cases, a consensus was reached; it was, therefore, not necessary to consult a third reviewer during the screening and selection process.

TABLE 12 The AG's review of economic evidence: inclusion criteria

Criteria	Inclusion
Population	Adults with progressive, locally advanced or metastatic RR-DTC
Intervention	• Lenvatinib • Sorafenib
Comparators	• Lenvatinib • Sorafenib • BSC
Costs	Direct health-care costs
Outcomes	Incremental cost per life-year gained and/or incremental cost per QALY gained
Study design	Full economic evaluations that consider both costs and consequences (cost-effectiveness analysis, cost–utility analysis, cost-minimisation analysis and cost–benefit analysis)
Date span	1999 to 10 January 2017
Language	English language only

Quantity of evidence

The searches for economic evidence identified 19 citations in total: 14 were obtained from the database searches and five were identified from other sources. Once duplicates were removed, 18 publications remained and, after assessment of the titles and abstracts, 10 publications[5,38,48,158–164] were retrieved and a detailed assessment of their eligibility was undertaken.

Nine of these 10 publications were included in the review. The AG included four publications[158–160,163] that clearly met the inclusion criteria. The AG considered that the economic evidence for lenvatinib and sorafenib that had been submitted to the SMC[38,48] and CADTH[5,162] was also relevant to this review and so these four records,[5,38,48,162] one for each drug's individual submission to each regulatory agency, were included in the review. One further relevant publication[161] was identified during the citation search of the included publications; this publication became available online only after the AG's database searches had been completed.

One publication[164] was a budget impact analysis and was, therefore, excluded from the review.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of study selection is shown in *Figure 8*.

A summary of the characteristics of the nine included publications[5,38,48,158–163] is presented in *Table 13*.

Quality of the included evidence

The quality of the included evidence was assessed using the NICE reference case checklist[169] and the Drummond checklist.[170] Summary tables of the AG's quality assessments are presented in *Appendices 11* (see *Table 72*) and *12* (see *Table 73*). Full details of the completed checklists are presented in *Appendices 13* (see *Tables 74–81*) and *14* (see *Tables 82–89*). The publications by Huang *et al.*[158,159] have been evaluated together as the same economic model was used to generate results for both publications.

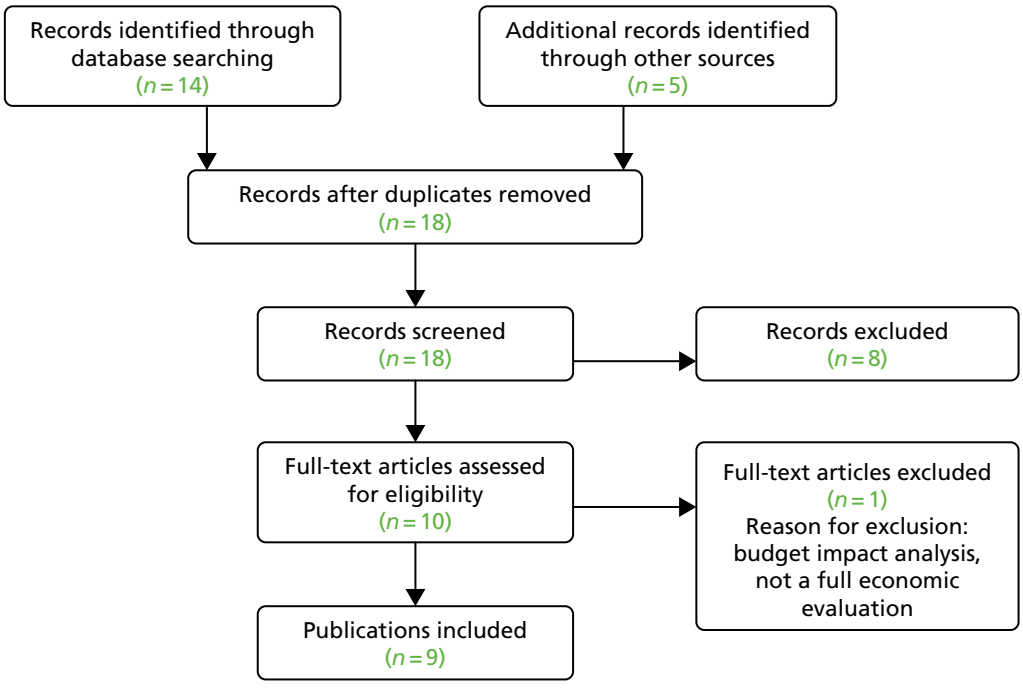

FIGURE 8 The PRISMA flow diagram: the AG economic literature review.

TABLE 13 Characteristics of publications included in the AG's review of economic evidence

Study	Characteristic								
	Country; perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/outcome source	Time horizon/ cycle length/ discount rate	Cost year	Further information on publication type
Erdal *et al.* 2015[163]	Turkey; Turkish health-care system	Sorafenib	Cost-effectiveness/ utility analysis	BSC	QALYs and LYs; costs calculated in Turkish lira and converted (2.2) to US$	Clinical inputs from DECISION Resource use via expert panel	Time horizon: lifetime (maximum 30 years) Cycle length: 28-days Discount rate: NR	Mid-2014	Abstract only
Huang *et al.* 2016[158]	USA; US health-care system	Lenvatinib, sorafenib	Cost–utility analysis	Placebo and each other	QALYs; costs in US$	Effectiveness estimates taken from DECISION and SELECT Costs and utilities from RED BOOK Online® (Truven Health Analytics, IBM Micromedex®, Ann Arbor, MI, USA, Chicago, IL, USA and Denver, CO, USA), Healthcare Cost and Utilization Project (Agency for Healthcare Research and Quality, Rockville, MD, USA), Medicare Fee Schedule (US Department of Health and Human Services, Centers for Medicare and Medicaid Services, Baltimore, MD, USA) and published literature (additional references NR)	Time horizon: lifetime Cycle length: bimonthly Discount rate: 3%	2015	Abstract only
Huang *et al.* 2016[159]	USA; US health-care system	Lenvatinib, sorafenib	Expected value of perfect information analysis	Placebo and each other	ICER per QALY and EVPI per person; costs in US$	Effectiveness estimates taken from DECISION and SELECT Costs and utilities from RED BOOK Online®, Healthcare Cost and Utilization Project, Medicare Fee Schedule and published literature (additional references NR)	Time horizon: lifetime Cycle length: bimonthly Discount rate: 3%	2015	Abstract only

continued

TABLE 13 Characteristics of publications included in the AG's review of economic evidence (*continued*)

Study	Characteristic								
	Country; perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/outcome source	Time horizon/ cycle length/ discount rate	Cost year	Further information on publication type
Tremblay *et al.* 2016[160]	USA; US health-care system	Lenvatinib sorafenib	Cost-effectiveness/ utility analysis	Each other	Costs and QALYs, cost per PFS year, cost per LY, cost per QALY, cost per responder; costs in US$	IHS global pricing database,[165] CMS database[166] and published sources Kerr *et al.*[167] is the source of EQ-5D utilities	Time horizon: 10 years (5-year horizon outcomes also reported) Cycle length: 1 month Discount rate: 5% [via correspondence with author: Dr Gabriel Tremblay, Purple Squirrel Economics (previously at Eisai Ltd), June 2017]	Not fully reported but states that the costs used to estimate BSC are from 2014 2014 used as cost year for currency conversion estimate	Abstract and accompanying poster and correspondence with author
Wilson *et al.* 2017[161]	USA; US health-care system	Lenvatinib, sorafenib	Cost–utility analysis	Placebo and each other	QALYs; costs in US$	Effectiveness estimates taken from DECISION and SELECT Costs and utilities from RED BOOK Online®, Healthcare Cost and Utilization Project, Medicare Fee Schedule and published literature, including Fordham *et al.*[168] for utilities	Time horizon: lifetime Cycle length: bimonthly Discount rate: 3%	2015	Peer-reviewed journal article
SMC 2015[48]	Scotland; Scottish NHS	Sorafenib	Cost–utility analysis	BSC	ICER per QALY; costs in Great British pounds	Rates of effectiveness and resource use from DECISION	Time horizon: not explicitly stated, but text implies that it is > 15 years Cycle length: NR Discount rates: NR	NR – 2015 used as cost year for currency conversion estimate	Summary of model and submission to the SMC

TABLE 13 Characteristics of publications included in the AG's review of economic evidence (*continued*)

Study	Characteristic								
	Country; perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/outcome source	Time horizon/ cycle length/ discount rate	Cost year	Further information on publication type
SMC 2016[38]	Scotland; Scottish NHS	Lenvatinib	Cost–utility analysis	BSC and sorafenib	ICER per QALY, incremental LYs; costs in Great British pounds	Effectiveness and resource use evidence from SELECT and DECISION	Time horizon: lifetime Cycle length: NR Discount rates: NR	NR – 2016 used as cost year for currency conversion estimate	Summary of model and submission to the SMC
CADTH 2015[5]	Canada; Canadian health-care system	Sorafenib	Cost–utility analysis	BSC	ICER per QALY; incremental costs, QALYs and LYs; costs in CA$	NR	Time horizon: 10-year base-case horizon (re-estimated at 7 years for main results) Cycle length: NR Discount rates: NR	NR – 2015 used as cost year for currency conversion estimate	Summary of model and submission to CADTH
CADTH 2016[162]	Canada; Canadian health-care system	Lenvatinib	Cost–utility analysis	BSC and sorafenib (results reported for BSC comparison only)	ICER per QALY; incremental costs, QALYs and LYs; costs in CA$	Effectiveness data from SELECT and DECISION	Time horizon: 10-year base-case horizon (re-estimated at 7 years for main results) Cycle length: 30.4 days Discount rate: NR	2016	Summary of model and submission to CADTH

CMS, Centres for Medicare and Medicaid Services; EVPI, expected value of perfect information; ICER, incremental cost-effectiveness ratio; LY, life-year; LYS, life-year saved; NR, not reported.

Only the Wilson *et al.*[161] publication was available as a full-text paper published in a peer-reviewed journal. Three of the included publications[158,159,163] were available only as abstracts, and one publication[160] was available as a poster. The submissions to the regulatory bodies in Scotland[38,48] and Canada[5,162] were available only as summary reports. As a result, only limited information was available from most of the included publications and this hindered the quality assessment of some of the methodologies described in the publications.

The authors of all of the included publications produced incremental cost-effectiveness estimates enabling a single metric [an incremental cost-effectiveness ratio (ICER) per QALY gained] to be used for comparative purposes. All of the publications included a discussion of the certainty associated with study results; however, full details of the sensitivity analyses and parameter values were not always available in the text.

Generally, the text describing the assumptions and data sources used to generate resource use, costs and HRQoL estimates within the economic models was not clear. In addition, it was unclear whether or not the costs and benefits described in the publications were discounted appropriately. Results from analyses of the cost-effectiveness of all the relevant comparators (lenvatinib, sorafenib and BSC) were available from only four of the reviewed publications.[158–161]

None of the publications considered the decision problem from the perspective of the NHS in England. However, as the Scottish NHS provides a sufficiently similar environment to the NHS in England, the AG considered that, for the purposes of this appraisal, the results from the SMC submissions[38,48] are broadly generalisable to patients in England. The characteristics of the health-care systems, in terms of the way treatments are procured and used in the USA,[158,159,161] Canada[5,162] and Turkey,[163] make the results from analyses based on these perspectives less useful when considering treatment options for patients in the NHS in England. However, including these studies[5,158,159,161–163] in this review allows a broad range of cost-effectiveness estimates to be considered and provides some indication of the effect of varying assumptions, such as the model time frame and estimates of HRQoL.

Assessment Group economic review: overview of included publications

The AG identified nine relevant publications[5,38,48,158–163] describing the cost-effectiveness of treatment with lenvatinib and sorafenib in a population of patients with RR-DTC. When necessary, authors were contacted and asked to provide further information on methodological aspects that lacked clarity in the publications; only one lead author[160] replied and provided the discount rate used in the model.

One publication[163] considered the cost-effectiveness of treatment with sorafenib compared with usual care in the Turkish setting. Four publications[158–161] compared treatment with lenvatinib with treatment with sorafenib from a US perspective. The SMC submissions[38,48] considered resource use in the Scottish NHS, and the CADTH submissions[5,162] included analyses that were undertaken from the perspective of the Canadian health-care system. The results reported in the publications[5,38,48,158–162] comparing the cost-effectiveness of lenvatinib with the cost-effectiveness of sorafenib are based on the results of indirect comparisons. This means that the authors considered that the trial and patient characteristics of SELECT and DECISION were sufficiently comparable for their data to be compared using this methodology. The AG discusses the limitations of using data from SELECT and DECISION in an indirect comparison in *Chapter 4*, *Indirect comparison feasibility assessment*.

The costs, benefits and incremental results from each of the publications are presented in *Table 14*. All costs from 2014 have been inflated to 2015/16 prices using the hospital and community health services index.[171] Analyses conducted using 2015 and 2016 prices have not been inflated as the 2016/17 inflation indices were not available. When the year that costs used within the model is not reported, the year of publication is used as a proxy. When necessary, all cost data have been converted to Great British pounds using the Bank of England exchange rate as of 25 May 2017.[172]

TABLE 14 Results of publications that were included in the AG's review of economic evidence

					Incremental			ICER (£)	
Study	Interventions	Costs (£)	LYs	QALYs	Costs (£)[a]	LYs	QALYs	Per LY gained	Per QALY gained
Erdal *et al.* 2015[163]	BSC	NR	NR	NR					
	Sorafenib	NR	NR	NR	19,084	1.29	0.80	14,754	23,859
Huang *et al.* 2016[158]	Placebo	657,493	NR	NR					
	Lenvatinib	152,448	NR	NR	–505,045 (vs. BSC) 25,491 (vs. sorafenib)	NR	NR	NR	61,109 (vs. sorafenib)
	Sorafenib	126,957	NR	NR	–530,536 (vs. BSC)	NR	NR	NR	
Huang *et al.* 2016[159]	Lenvatinib vs. sorafenib	NR	NR	NR		NR	NR	NR	73,913
[b]Tremblay *et al.* 2016[160]	Lenvatinib	217,527	2.71	1.77	40,697	0.33	0.42	124,843	96,671
	Sorafenib	176,830	2.38	1.35					
[c]Tremblay *et al.* 2016[160]	Lenvatinib	228,637	3.38	2.10	44,626	0.58	0.54	76,835	81,338
	Sorafenib	184,010	2.80	1.56					
Wilson *et al.* 2017[161]	Placebo	107,898	NR	0.71					
	Lenvatinib	127,819	NR	1.34	7368 (vs. sorafenib) 19,921 (vs. placebo)	NR	0.37 (vs. SOR) 0.63 (vs. placebo)	NR	19,522 (vs. sorafenib) 31,566 (vs. placebo)
	Sorafenib	120,451	NR	0.96	12,553 (vs. placebo)	NR	0.25 (vs. placebo)	NR	49,484 (vs. placebo)

continued

TABLE 14 Results of publications that were included in the AG's review of economic evidence (*continued*)

					Incremental			ICER (£)	
Study	Interventions	Costs (£)	LYs	QALYs	Costs (£)[a]	LYs	QALYs	Per LY gained	Per QALY gained
SMC 2015[48]	Sorafenib vs. BSC	NR	NR	NR	NR	NR	NR	NR	32,083
SMC 2016[38]	Lenvatinib vs. sorafenib	NR	NR	NR	NR	NR	NR	NR	49,525
[d]CADTH 2015[5]	Sorafenib vs. BSC	NR	NR	NR	42,824	0.86	0.52	49,795	82,080
[e]CADTH 2015[5]	Sorafenib vs. BSC	NR	NR	NR	45,744 to 46,054	NR	0.38–0.42	NR	108,974 to 118,913
[d]CADTH 2016[162]	Lenvatinib vs. BSC	NR	NR	NR	60,784	1.01	0.84	60,182	72,536
[e]CADTH 2016[162]	Lenvatinib vs. BSC	NR	NR	NR	84,687	1.03	0.84	98,343	101,293

NR, not reported; LY, life-year.
a All costs were inflated to 2015/16 and were converted to Great British pounds.
b 5-year horizon.
c 10-year horizon.
d Submitted analysis.
e Reanalysis by Economic Guidance Panel.

Erdal *et al.*[163]

The authors described a partition survival model that used clinical evidence from DECISION, supplemented with Turkey-specific resource use and cost information, to generate estimates of the cost-effectiveness of treatment with sorafenib versus BSC in a population of people with locally advanced or metastatic RR-DTC. Deterministic results were presented and the ICER per QALY gained for the comparison of treatment with sorafenib with treatment with BSC was £23,859. The authors concluded that the results of the one-way deterministic analyses and probabilistic sensitivity analysis (PSA) were similar to the main set of deterministic results. However, as few details of the parameters and values that were used to estimate the level of uncertainty around results were reported in the publication, the AG was not able to ascertain the reliability of results generated by the sensitivity analyses. Despite not reporting a willingness-to-pay threshold, the authors considered sorafenib to be a cost-effective treatment compared with BSC.

Huang *et al.*[158]

The Markov model described by the authors used effectiveness evidence from the Phase III trials SELECT and DECISION. Results from one-way sensitivity analyses showed that the base-case model results were sensitive to changes to the costs of lenvatinib and sorafenib and the utility benefit of continuing with lenvatinib. The AG notes that the value and duration of the utility benefits were not reported. The base-case ICER for the comparison of treatment with lenvatinib with treatment with sorafenib was £61,109 per QALY gained.

Huang *et al.*[159]

The authors reported the methods and results of an expected value of perfect information (EVPI) analysis using the same model described in the abstract by Huang *et al.*[158] An ICER of £73,913 per QALY gain was reported, indicating that treatment with lenvatinib offers an increase in benefit over sorafenib, but at an additional cost. At a willingness-to-pay threshold of approximately £77,000 per QALY gained, the probabilities of lenvatinib and sorafenib being cost-effective were low (37% and 33%, respectively). Owing to uncertainty around the reliability of model results, the authors were not certain that treatment with lenvatinib was cost-effective when compared with sorafenib and placebo.

Tremblay *et al.*[160]

The poster included results from a cost-effectiveness analysis from a partition survival model designed to compare treatment with lenvatinib and treatment with sorafenib using clinical evidence from the Phase III SELECT and DECISION. The base-case ICER for the comparison of treatment with lenvatinib with treatment with sorafenib was £81,338 per QALY gained when a 10-year time horizon was modelled, and £96,671 per QALY gained when a 5-year time horizon was modelled.

Costs per PFS year (£58,833 with a 5-year time horizon and £62,318 with a 10-year time horizon), costs per responder (£77,372 with a 5-year time horizon and £84,841 with a 10-year time horizon) and life-year saved were also reported in the publication. The authors did not set a willingness-to-pay threshold to determine at what level the cost per responder, for example, would offer good value for money. The authors refer to PSA in the publication but do not report the methods or the results of the analysis.

Wilson *et al.*[161]

The same set of authors who produced the abstracts by Huang *et al.*[158,159] authored a full-text paper comparing the cost-effectiveness of treatment with lenvatinib with that of sorafenib, in which they described a Markov model that used effectiveness data from the Phase III trials SELECT and DECISION. ITCs to compare the effectiveness of lenvatinib with the effectiveness of sorafenib were made following adjustments to the placebo arms of the trials as the authors considered that the placebo arm of SELECT included patients who appeared to be healthier than those in the comparator arm of DECISION. However, the AG does not consider that the adjustments are sufficient to generate reliable estimates of the comparative effectiveness of lenvatinib and sorafenib. In addition, as discussed in *Chapter 4*, *Indirect comparison feasibility assessment*, the AG does not consider that it is appropriate to undertake an indirect comparison of the effectiveness of lenvatinib and the effectiveness of sorafenib using data from SELECT and DECISION.

The results of the authors' cost–utility analysis differ from those reported in the abstracts.[158,159] In the base-case analysis, treatment with lenvatinib generated more benefits (+ 1.34 QALYs) than treatment with sorafenib (+ 0.96 QALYs), as well as more benefits than placebo (+ 0.71 QALYs), but at an increased cost of £7368 versus sorafenib and £19,921 versus placebo. The base-case ICER for the comparison of treatment with lenvatinib with treatment with sorafenib was £19,522 per QALY gained. The base-case ICERs for the comparison of treatment with lenvatinib with placebo and treatment with sorafenib with placebo were £31,566 and £49,484 per QALY gained, respectively.

Sorafenib Scottish Medicines Consortium submission[48]

For the comparison of treatment with sorafenib with BSC, the ICER was £32,083 per QALY gained; the Scottish PAS price of sorafenib was used in the analysis.[48] These results were sensitive to the time horizon of the model and the approach used to estimate OS, with the ICER increasing with a shortened time horizon and with a change to the OS extrapolation method employed.

Lenvatinib Scottish Medicines Consortium submission[38]

For the comparison of treatment with lenvatinib with treatment with sorafenib, the base-case ICER was £49,525 per QALY gained; this analysis used the Scottish PAS price for lenvatinib and Eisai Ltd's estimate of the Scottish PAS discount currently in place for sorafenib.[38] The ICERs per QALY gained were sensitive to the estimates of OS for lenvatinib (ranged from £29,000 to £96,000 per QALY gained with PAS prices) and to changing the utility rates used in the model by 20% (ranged from £41,000 to £62,000 per QALY gained with PAS prices).

Sorafenib Canadian Agency for Drugs and Technologies in Health submission[5]

The company's base-case cost-effectiveness estimate was that treatment with sorafenib versus BSC resulted in an ICER of £82,080 per QALY gained. Several other ICERs per QALY gained were also presented as a result of reanalyses suggested by the Economic Guidance Panel. The reanalyses included amendments to the time horizon, the duration of treatment and estimates of OS. The results from the reanalyses ranged from £108,974 to £118,913 per QALY gained.

Lenvatinib Canadian Agency for Drugs and Technologies in Health submission[162]

The base-case analysis for the comparison of lenvatinib with BSC, submitted by the company, generated an ICER of £72,536 per QALY gained. This increased to £101,293 per QALY gained when the amendments suggested by the Economic Guidance Panel were implemented. The reanalysis included amendments to OS estimates, time horizon, use of the intervention drug in terms of both wastage and the appropriate pack size to reach the required dosage, and the utility values used within the model.

Although the company submitted results from additional analyses comparing the cost-effectiveness of lenvatinib with the cost-effectiveness of sorafenib to CADTH, these results were not presented in the available CADTH guidance report.[162]

The AG notes that the SMC[38,48] and CADTH[5,162] reports highlight concerns about the clinical effectiveness data derived from SELECT and DECISION. Key issues of concern related to median OS not being reached and the high rates of treatment crossover from the placebo (BSC) arms to the intervention arms (lenvatinib or sorafenib) that took place during the trials.

The Assessment Group's review of economic evidence: summary and conclusions

The published economic evidence[163] shows that the ICER of £23,859 per QALY gained for the comparison of sorafenib with BSC (after conversion from Turkish lira) is within the willingness-to-pay threshold that is considered to reflect a cost-effective use of NHS resources. However, without further details of the economic model inputs, in particular the resource use and costs, the relevance of this finding to the NHS setting is unclear.

In the US setting, when compared with placebo, both treatment with lenvatinib and treatment with sorafenib appear to provide additional health benefits while either saving resources[158] or yielding ICERs per QALY gained of < £50,000 after conversion from US$ (£31,566 per QALY gained[161] for lenvatinib versus placebo and £49,484 per QALY gained[161] for sorafenib vs. placebo). When treatment with lenvatinib is compared with sorafenib in the US setting, lenvatinib offers a health benefit over sorafenib but at an increased cost. Cost-effectiveness results ranged from £19,522 per QALY gained[161] (lenvatinib vs. sorafenib) to £96,671 per QALY gained[160] (lenvatinib vs. sorafenib), at current UK prices. Again, it is unclear whether or not these results are relevant to the NHS setting.

In 2015, sorafenib became the standard of care for patients in Scotland with locally advanced or metastatic RR-DTC, provided that the company supplied the drug to the NHS at the Scottish PAS price agreed by the company with NHS Scotland.[48] The SMC sorafenib report[48] states that sorafenib generated more benefit than BSC but at an increased cost. The ICER for this comparison was £32,083 per QALY gained. In 2016, an appraisal of treatment with lenvatinib[38] versus sorafenib was submitted to the SMC; lenvatinib was considered by the SMC to be both an orphan drug and an end-of-life treatment. For the comparison of treatment with lenvatinib with treatment with sorafenib, based on survival outcome results generated using indirect comparison methods, and using the Scottish PAS price for lenvatinib, the ICER per QALY gained was estimated to be £49,525 and lenvatinib was accepted for use in NHS Scotland.

The AG notes that any discount to the list prices of the drugs agreed with the NHS in Scotland does not equate to an equivalent agreement with the NHS in England. All PAS prices are confidential and thus the applicability of the results presented within the Scottish submissions to the appraisal of lenvatinib and sorafenib for use in the NHS in England is unclear as it is not known whether or not the discounts agreed with the NHS in Scotland are the same as those agreed with the NHS in England.

In 2015, sorafenib was appraised by CADTH[5] and, after reanalyses suggested by the Economic Guidance Panel, estimates of the most plausible ICERs for the cost-effectiveness of treatment with sorafenib versus BSC ranged from £108,974 to £118,913 per QALY gained (after conversion from CA$). Lenvatinib was considered for use by the Canadian health-care system in 2016. Estimates of the cost-effectiveness of treatment with lenvatinib versus both BSC and sorafenib were generated but only the comparisons with BSC are reported in the CADTH report.[162] After the Economic Guidance Panel's suggested amendments were carried out, the best estimate for the comparison of treatment with lenvatinib versus BSC was £101,293 per QALY gained. Both lenvatinib and sorafenib have been recommended for use in Canada. The relevance of these results to patients in the NHS is unknown.

What is lacking from the current evidence base are any cost-effectiveness analyses of direct relevance to the NHS in England. The SMC submissions[38,48] provide an insight into the costs and consequences associated with treatment with lenvatinib, sorafenib and BSC, and these are likely to be similar for patients treated in England. However, the PAS prices agreed with the NHS in Scotland are confidential and this prevents the reported cost-effectiveness estimates being directly applicable to the NHS in England.

Head-to-head comparisons of the effectiveness of treatment with lenvatinib with the effectiveness of treatment with sorafenib depend on results from indirect comparisons, whether conducted in a formal statistical framework[5,38,48,160,162] or with adjustments made to the placebo arms of the Phase III trials,[161] which provide estimates based on the pooling of the comparator arms within the SELECT and DECISION Phase III trials. The AG considers that, because of the issues discussed in *Chapter 4*, *Indirect comparison feasibility assessment*, it is not appropriate to employ indirect comparisons of the effectiveness of lenvatinib and the effectiveness of sorafenib using data from SELECT and DECISION.

Summary of the companies' systematic reviews of economic evidence

Both of the companies carried out systematic reviews to identify published cost-effectiveness studies that included lenvatinib and/or sorafenib. Both companies concluded that there are no cost-effectiveness studies conducted in the UK from the perspective of the NHS that were relevant to decision-making in England. Therefore, both companies produced their own de novo economic evaluations.

Summary of the key features of the companies' economic models

This section includes summary details of the key features of the economic models submitted to NICE, from Eisai Ltd and Bayer HealthCare, as part of the MTA process. All of the company data presented in this section are drawn from the company submissions[7,8] and models.

Population

Both companies state that their economic evaluations focus on patients with progressive RR-DTC. However, in the submission from Eisai Ltd,[8] it is highlighted that the SELECT definition of progressive RR-DTC was locally advanced or metastatic DTC confirmed by radiographic evidence of disease progression within the prior 13 months and that some patients participating in this trial had received prior vascular endothelial growth factor (VEGF) therapy. Eisai Ltd[8] points out that, in contrast, no patients recruited to DECISION had received prior VEGF therapy and that, to be eligible for recruitment, evidence of disease progression within the 14 months prior to commencing the trial was required. The AG describes other differences in the two trial populations in *Chapter 4*, *Trial characteristics*, *Participant characteristics* and *Indirect comparison feasibility assessment*.

Model structure

Key elements of the structure of the economic models submitted by Eisai Ltd and Bayer HealthCare are included in *Table 15*. The structure of the two company models is similar and is in line with the structure of models that have previously been submitted to NICE to inform appraisals of interventions used to treat patients with cancer. The structure of both models conforms to specifications detailed in the final scope issued by NICE.[53]

TABLE 15 Model structure

Parameter	Eisai Ltd's model (lenvatinib)	Bayer HealthCare's model (sorafenib)
Intervention	Lenvatinib	Sorafenib
Comparators	• Sorafenib • Placebo/BSC	• Lenvatinib • Placebo/BSC
Model structure	A four-state (stable disease, response, progressive and death) partitioned survival cost–utility model developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA)	A three-state (progression-free, progressed and death) partitioned survival cost–utility model developed in Microsoft Excel®
Cycle length	1 month (30.43 days)	28 days
Model time horizon	33.35 years (5 years and 10 years are considered as scenario analyses)	30 years
Discounting	Costs and benefits were discounted at a rate of 3.5% annually in line with the NICE reference case[169]	
Perspective	The perspective is stated to be that of the NHS and PSS. However, no specific PSS elements are considered to be relevant to the RR-DTC population and none is included in either model	

PSS, Personal Social Services.
Note
Information drawn from Eisai Ltd[8] (section 5.2) and Bayer HealthCare[7] (section 4.2).

Therapies

Details about the intervention and comparators included in the company models are provided in *Table 16*. Both models included the therapies listed in the final scope issued by NICE.[53] The AG highlights that the lenvatinib and sorafenib doses in the models are based on average levels of use in SELECT and DECISION and are lower (approximately 17 mg for lenvatinib and 651 mg for sorafenib) than the licensed doses (24 mg for lenvatinib and 800 mg for sorafenib). Possible reasons include dose interruptions/reductions as a result of AEs; in some cases, intolerance may lead to a treatment being stopped.

Survival modelling

Summary details of the general approach the companies used to model patient survival (OS and PFS) are provided in *Tables 17* and *18*, respectively.

Measurement and valuation of health effects

Sources of utility values

The base-case utility values used in the Eisai Ltd model were stated to be taken from EQ-5D values for sorafenib from DECISION. Disutilities were then applied as a weighted proportion, based on values obtained from a vignette study carried out by Fordham *et al.*[168] The AG notes that only the utility values used in the progressive state were the same as the utility values derived from DECISION.

The source of the utility values used in the Bayer HealthCare model[7] was the EQ-5D data collected during DECISION. No additional utility decrements associated with AEs were included in the model.

The use of utility values derived from EQ-5D data collected during clinical trials is in line with the approach set out in the NICE *Guide to the Methods of Technology Appraisal 2013*.[169]

TABLE 16 Modelled therapies

Parameter	Eisai Ltd's model (lenvatinib)	Bayer HealthCare's model (sorafenib)
Lenvatinib	Price: list price used in the CS; however, a completed PAS submission template was made available to the ERG during the review period Daily dose: 17.4 mg (based on SELECT data, Eisai Ltd[8]). Treatment duration: SELECT TTD data	Price: list price Daily dose: 17.4 mg (based on published data;[8] estimate does not account for dose interruption) Treatment duration: the sorafenib TTD K–M data were adjusted to fit the SELECT median duration of treatment
Sorafenib	Price: MiMS price Daily dose: 651 mg (based on data from DECISION) Treatment duration: assumed until disease progression	Price: CMU price Daily dose: 651 mg (based on data from DECISION) Treatment duration: DECISION TTD K–M data (these data are complete and, therefore, no extrapolation was required)
Placebo/BSC	Assumption: no additional costs	BSC is defined as concurrent use of radiotherapy (10.6% in the sorafenib arm and 21.4% in the placebo arm of DECISION)
Administration cost	Deliver oral chemotherapy (SB11Z): £183.50	None
Subsequent therapies	None (assumption based on expert advice)	

CMU, Commercial Medicines Unit; CS, company submission; ERG, Evidence Review Group; MiMS, Monthly Index of Medical Specialities; TTD, time to treatment discontinuation.
Note
Information drawn from Eisai Ltd[8] (section 5.2) and Bayer HealthCare[7] (section 4.2).

TABLE 17 Overall survival modelling

Model	Lenvatinib	Sorafenib	Placebo/BSC
Eisai Ltd	SELECT data from third data cut-off point (August 2015) extrapolated using piecewise exponential curve	The curve, generated to represent OS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC using data from the third data cut-off points of DECISION and SELECT (July 2015 and August 2015, respectively)	SELECT data from third data cut-off point (August 2015), recensored and RPSFTM-adjusted, and extrapolated using piecewise exponential curve
Bayer HealthCare	The curve, generated to represent OS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC using data from the second data cut-off points of SELECT and DECISION (June 2014 and May 2013, respectively)	DECISION data from second data cut-off point (May 2013) allowed a direct comparison. The data were extrapolated using an exponential distribution	DECISION-adjusted ITT data from second data cut-off point (May 2013) allowed a direct comparison. The data were extrapolated using an exponential distribution

Note
Information drawn from Eisai Ltd[8] (section 5.3) and Bayer HealthCare[7] (section 4.3).

TABLE 18 Progression-free survival modelling

Model	Lenvatinib	Sorafenib	Placebo/BSC
Eisai Ltd	SELECT data from first data cut-off point (November 2013) extrapolated using piecewise gamma curve	The curve, generated to represent PFS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC using data from the third data cut-off points of DECISION and SELECT (July 2015 and August 2015, respectively)	Not affected by crossover – SELECT data from first data cut-off point (November 2013) extrapolated using piecewise gamma curve
Bayer HealthCare	The curve, generated to represent PFS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC using data from SELECT and DECISION	DECISION data from second data cut-off point (May 2013) allowed a direct comparison. The data were extrapolated using an exponential distribution	DECISION data (May 2013 data cut-off point) allowed a direct comparison. The data from each arm were extrapolated using exponential distributions

Note
Information drawn from Eisai Ltd[8] (section 5.3) and Bayer HealthCare[7] (section 4.3).

Utility values

The utility values used in the companies' models are provided in *Table 19*.

Health-care costs

Levels of resource use

Eisai Ltd obtained estimates of the level of health-care utilisation inputs for the pre-progression and progressive disease states from physician surveys conducted in Europe; these estimates were then validated by four practising clinical experts employed by NHS England. Mortality-related costs were obtained from the Nuffield Trust[173] and adjusted for inflation to 2016 values based on PSSRU[171] inflation rates for 2016.

TABLE 19 Utility values

Health state	Lenvatinib	Sorafenib	Placebo/BSC
Eisai Ltd's model			
Stable disease	0.76	0.68	0.77
Response	0.82	0.74	0.83
Progressive	0.64	0.64	0.64
Bayer HealthCare's model			
Progression-free	0.72 (SE 0.08)	0.72 (SE 0.08)	0.8 (SE 0.07)
Post progression	0.64 (SE 0.06)	0.64 (SE 0.06)	0.64 (SE 0.06)

SE, standard error.
Note
Information drawn from Eisai Ltd[8] (table 18) and Bayer HealthCare[7] (table 27).

Expert advice from oncologists was the basis for Bayer HealthCare's resource use estimates. Unit costs were obtained from the *NHS Reference Costs 2015 to 2016*[174] and the *Unit Costs of Health and Social Care 2016*.[171] In the model, it is assumed that resource use associated with treatment with lenvatinib is the same as the resource use associated with treatment with sorafenib.

The monthly routine care costs used in both company models are provided in *Appendix 10* (see *Table 70*).

Eisai Ltd's routine costs included physician visits and disease-associated hospitalisation days. Bayer HealthCare's routine costs included inpatient stay, outpatient appointments and pharmaceutical costs.

Eisai Ltd's end-of-life costs (£7450) included secondary care, local-authority-funded social care, district nursing and GP contacts.

Adverse event costs

The Eisai Ltd model includes the following AEs:

- lenvatinib – grade 3 and 4 treatment-emergent AEs and AEs that required hospitalisation in SELECT
- sorafenib – grade 3 and 4 treatment-emergent AEs in DECISION and AEs that required hospitalisation based on proportions from SELECT.

The Bayer HealthCare model[7] only includes grade 3 and 4 AEs occurring in > 5% of patients in the lenvatinib arm of SELECT or in the sorafenib arm of DECISION.

Bayer HealthCare also included AE management costs (per 28 days), see table 29 in the company submission for details.[7]

Frequencies/rates and costs associated with AEs included in the company models are presented in *Appendix 10* (see *Table 71*). Eisai Ltd's cost sources are a mix of *NHS Reference Costs 2015 to 2016*[174] and *Unit Costs of Health and Social Care 2016*.[171] Bayer HealthCare's cost sources are a mix of *NHS Reference Costs 2014 to 2015*,[175] *Unit Costs of Health and Social Care 2015*[176] and *British National Formulary* (BNF) costs.[47]

Cost-effectiveness results

Base-case cost-effectiveness results

The base-case cost-effectiveness results from the Eisai Ltd[8] and Bayer HealthCare[7] submitted economic models are shown in *Table 20*.

Bayer HealthCare also carried out cost-effectiveness analyses using the adjusted MAIC HRs. The effect on the company's ICERs was small. The resultant base-case ICERs per QALY gained for the comparison of treatment with sorafenib with BSC and the comparison of treatment with lenvatinib with BSC are commercial in confidence and cannot be reported.

Probability of being the most cost-effective

For the Eisai Ltd model, the PSA results suggest that, at a willingness-to-pay threshold of £50,000 per QALY gained, the probability of lenvatinib being more cost-effective than sorafenib or BSC is 60%.

For the Bayer HealthCare model,[7] the PSA results suggest that, at a willingness-to-pay threshold of £30,000 per QALY gained, the probability of sorafenib being cost-effective is 30%, the probability of BSC being cost-effective is 54% and the probability of lenvatinib being cost-effective is 16%.

The PSA results from the Eisai Ltd and Bayer HealthCare submitted economic models are shown in *Table 21*.

Sensitivity and scenario analyses

Both companies carried out a range of deterministic sensitivity analyses and scenario analyses.

In the Eisai Ltd model, for the comparison of lenvatinib and sorafenib, the two most influential parameters in the deterministic sensitivity analysis were OS HR versus sorafenib (lenvatinib dominates) and PFS HR versus sorafenib (£5000 to £35,000 per QALY gained). In the scenario analyses, the most influential parameters were the treatment duration for lenvatinib (treatment to progression rather than clinical trial duration; £71,978 per QALY gained) and the cut-off point for OS and PFS extrapolation (20 weeks for OS and PFS; £29,874 per QALY gained).

TABLE 20 Base-case pairwise comparisons

	Total			Incremental			ICER per QALY gained
Technology	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Deterministic
Eisai Ltd's model results							
Lenvatinib	107,182	4.34	3.18				
Sorafenib	82,839	3.18	2.10	24,342	1.16	1.08	£22,491
Placebo/BSC	42,115	2.80	1.84	65,067	1.54	1.34	£48,569
Bayer HealthCare's model results							
Placebo/BSC	CiC	3.49	2.35				
Sorafenib	CiC	4.79	3.16	CiC	1.30	0.81	CiC
Lenvatinib	CiC	5.92	4.04	CiC	1.12	0.88	CiC

CiC, commercial in confidence; LYG, life-year gained.
Note
Information drawn from Eisai Ltd[8] (table 31) and Bayer HealthCare[7] (table 38).

TABLE 21 The probabilistic cost-effectiveness results

Technology	Total, mean (95% CI)		Incremental		ICER/QALY gained (vs. BSC)	ICER/QALY gained
	Costs	QALYs	Costs	QALYs		
Eisai Ltd's model						
Lenvatinib vs. sorafenib	NS	NS	NS	NS	NS	£21,578
Lenvatinib vs. placebo/BSC	NS		NS	NS	NS	£48,683
Bayer HealthCare's model (all based on results of indirect comparison)						
BSC	CiC	2.41 (1.00 to 5.19)				
Sorafenib	CiC	3.25 (1.81 to 5.30)	CiC	0.84	CiC	CiC
Lenvatinib	CiC	4.11 (2.02 to 6.67)	CiC	0.86	CiC	CiC

CiC, commercial in confidence; NS, not stated.
Note
Information drawn from Eisai Ltd[8] (table 34) and Bayer HealthCare[7] (table 42).

In the Bayer HealthCare model, for the comparison of sorafenib and lenvatinib, the largest deviations from the base-case ICER per QALY gained were attributable to variation in the OS HR for lenvatinib and lower lenvatinib progression-free utility. The scenario analyses that had the biggest effects on the companies' cost-effectiveness results were the time horizon (reduction to 10 years) and lower lenvatinib progression-free utility. The ICERs per QALY gained for these analyses are commercial in confidence and cannot be reported here.

The Assessment Group's independent cost-effectiveness assessment

Model design

In common with the two companies, the AG has used a standard partitioned survival model structure, applied to the patient population specified in the final scope issued by NICE,[53] to consider the cost-effectiveness of treatment with lenvatinib and sorafenib compared with BSC (as represented by data from the placebo arms of SELECT and DECISION).

Two particular differences should be noted:

1. The AG has not included a separate health state for patients who respond to treatment. On clinical advice, the AG considers that there is little merit in this addition to the standard three-state structure (in which patients begin in the progression-free health state and, following assessed disease progression, transfer to the postprogression state in which they receive only BSC prior to death). For responding patients, who are mostly symptom-free, response alone is unlikely to have a measurable effect on patient-perceived quality of life/utility and has no effect on resource use.
2. The AG has designed a model that allows each intervention (lenvatinib and sorafenib) to be represented in its natural time metric: 30-day cycles for lenvatinib and 28-day cycles for sorafenib. This involved creating two parallel models using the same assumptions and model parameters, but each with its own placebo arm calibrated from its respective clinical trial data. Although not ideal, the AG has provided an illustrative structural sensitivity analysis (*Figure 9*) based on applying data from the counterfactual placebo arm of both trials to illustrate the extent of uncertainty involved in comparisons between the active treatments with the currently available clinical evidence. The reason for this unusual approach is to demonstrate non-equivalence of the placebo arms of the two clinical trials, which renders indirect comparison of the two treatments via a common comparator invalid (as discussed in *Chapter 4*, *Indirect comparison feasibility assessment*, and illustrated graphically in *Figure 9*).

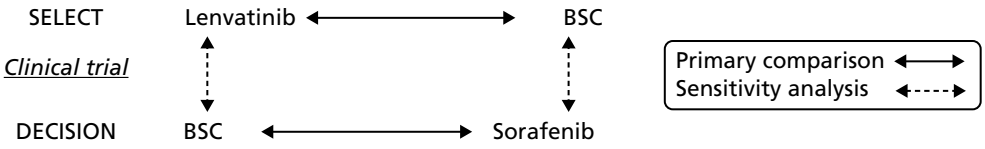

FIGURE 9 Model structure featuring two simple trial-based comparisons, with additional cross-trial comparisons as a structural sensitivity analysis to illustrate the uncertainty associated with choice of comparator.

Resource use estimation, the sources for unit costs and selection of health-related utility values used in the AG's model are presented in this section. Standard discount rates of 3.5% per annum are used for discounting both costs and benefits (measured as QALYs), but not for life-years (survival). The AG model is structured with a maximum time horizon of 40 years.

Effectiveness data

Modelling long-term outcomes from trial data

Both companies have followed a conventional approach to the general problem of identifying an appropriate method by which to extrapolate time-limited follow-up trial data for PFS, OS and time to treatment discontinuation. This involves attempting to fit a range of prespecified statistical functions to the available evidence, and selecting one that appears to be optimal according to particular 'measures of fit' (principally the Akaike information criterion and the Bayesian information criterion).

This paradigm is wholly dependent on the limited data available and the restricted armoury of 'standard' models. In particular, it fails to take into account a wider evidence base specifically related to the natural history of the disease, and the influence of particular characteristics of both the recruited patient group and of the trial design.

The AG has investigated long-term survival trends in patients diagnosed with Stage 3 or 4 (locally advanced or metastatic) thyroid cancer in the USA and recorded on the Surveillance Epidemiology and End Results (SEER) database.[177] A total of 32,818 patients (male and female) followed for 15 years yielded a persistent trend from 18 months after diagnosis. *Figure 10* demonstrates the very close match between these data and a simple linear model, indicating that the risk of death remained unchanged throughout this period, which is indicative of a simple exponential survival process.

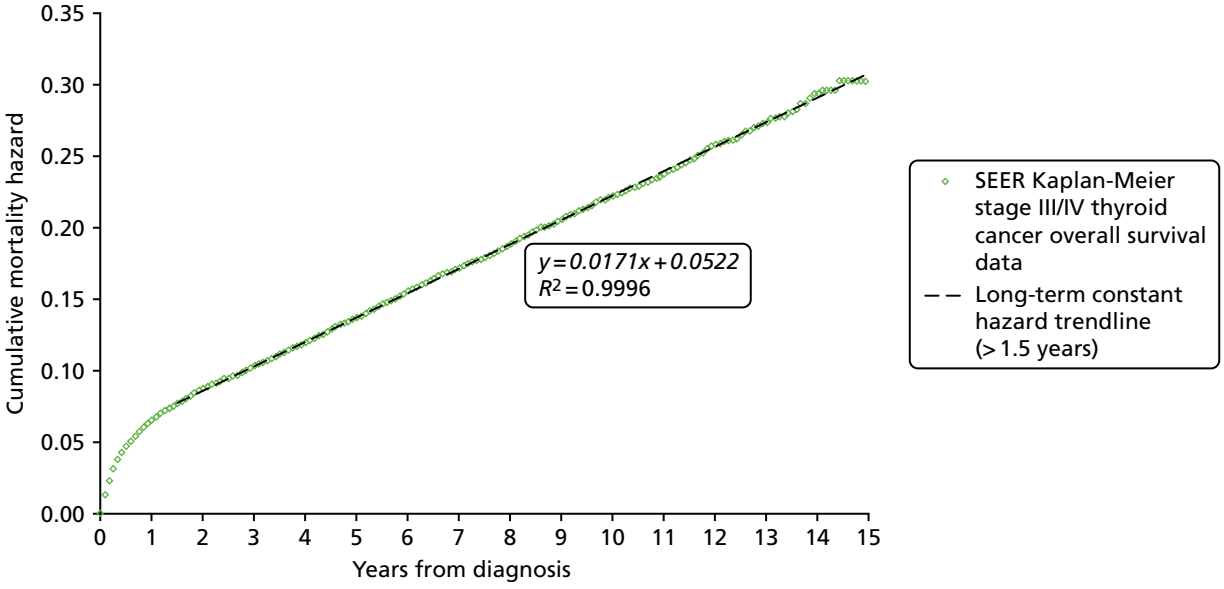

FIGURE 10 Cumulative hazard data from follow-up of patients diagnosed with stage III/IV thyroid cancer for 15 years.

This evidence is sufficiently compelling to give the AG confidence to employ exponential extrapolation as the default method of modelling incomplete trial data in this appraisal. The nature of clinical trials (selecting patients who have suffered a recent disease progression, and administering a novel treatment that takes time to reach full effectiveness) means that the initial period post randomisation will give rise to temporary distortions to the underlying disease process. However, thereafter, it is likely that the natural history of the condition will be re-established, so that a long-term exponential function will reappear. The mean time since diagnosis of patients randomised in DECISION was 7.24 years, suggesting that the trial cohort lies in the middle of the follow-up range shown in *Figure 10*. The AG is therefore confident that outcome data extrapolation should be focused on fitting exponential models to estimate lifetime survival expectation.

Data issues

Following the initial stakeholders' meeting for this appraisal (17 February 2017), the AG submitted identical requests to the two companies, asking for a set of detailed analyses of the latest data available from the two clinical trials, based on common analytical methods to allow comparative analyses to be carried out by the AG; thus, minimising the risk of methodological bias. Eisai Ltd provided the requested data relating to SELECT as an appendix to the submission.[8] Unfortunately, Bayer HealthCare chose not to address the AG's request. As a consequence, the AG was unable to conduct some comparative analyses based on common assumptions, and the potential for bias and uncertainty in the data available to the AG remains.

The two clinical trials that provide the effectiveness evidence for this appraisal share common features, which result in interpretive complexity and uncertainty. In particular, in both trials patients were permitted to cross over from the placebo control to the active treatment (lenvatinib or sorafenib) following disease progression. As a consequence, randomisation was broken in both trials and some outcome variables may not be mutually compatible, even after attempts to adjust for crossover effects.

Both companies assume that, in addition to the active treatments, a third comparator (BSC) may be represented by the placebo arms of the two trials. Moreover, it is implicitly assumed that the randomised patients are drawn from similar populations with reference to their risk profile for the various time-to-event outcomes measured [PFS, OS, postprogression survival (PPS) and time-to-treatment discontinuation]. In *Chapter 4*, *Indirect comparison feasibility assessment*, the non-equivalence of PFS data from the placebo arms of the two clinical trials has been clearly demonstrated. This is of crucial importance to attempts to employ relative effectiveness measures reliant on the PHs assumption in relation to PFS, which is the only standard outcome variable reported in these trials that is free from any contamination by crossover effects (both trial protocols required confirmation of disease progression before patients were allowed to enter the open-label phase in which patients in the placebo arm were offered crossover treatment).

The problem of devising a credible approach to indirect comparison between lenvatinib and sorafenib for PFS cannot be resolved by appeal to technical argument alone. The pattern of hazard over time for disease progression in the two active arms is sufficiently similar to justify a simple HR approach. However, the placebo arms exhibit unexpectedly inconsistent patterns of temporal change, not compatible with the assumption of similarity between the patient groups not receiving active treatment. The AG, therefore, considers that the patients enrolled in the two trials cannot be considered to derive from a common population. This degree of difference precludes the use of either placebo arm as being representative of untreated patients across both trials.

The data for both placebo arms exhibit an unexpected improvement in long-term survival (reducing progression hazard) for which there is no obvious explanation. The effect of this phenomenon is to produce a varying differential in performance when comparing survival components across the two trials without any clear confirmatory evidence. Therefore, the AG is unable to support the use of a conventional ITC in this appraisal. The AG considers that it is preferable to model the relative effectiveness and cost-effectiveness of each active treatment against its own placebo comparator, and then generate results for each drug relative to the placebo of the other clinical trial as a sensitivity analysis, in order to allow assessment of the uncertainty associated with the choice of comparator.

Progression-free survival

The AG chose to use data for locally assessed PFS rather than centrally assessed PFS, as local assessment is generally more closely related to normal clinical practice.

Lifetime mean PFS for patients in DECISION who received placebo may be readily estimated from trial data (for the period available) and a simple exponential curve that conforms closely to the reported trial data (*Figure 11*). The AG estimated lifetime mean PFS from the area under the K–M data to 16.5 months of elapsed time followed by the area under the exponential function thereafter, giving a lifetime mean PFS estimate of 7.56 months. The sorafenib PFS arm of DECISION exhibits a simple constant hazard (exponential) relationship (see *Figure 11*), allowing the lifetime mean PFS to be estimated in a similar fashion, using the area under the curve (AUC) of the K–M data until 25 months, and the exponential extrapolation thereafter. This shows a lifetime mean PFS estimate of 47.18 months for patients receiving sorafenib, and a mean gain in PFS of 39.62 months compared with receiving placebo.

The SELECT data for PFS exhibit a more complex pattern in each arm. The cumulative hazard plots (*Figure 12*) reveal two distinct phases, both of which follow a constant hazard. Patients in the placebo arm who remain progression-free after 312 days experience a reduction in hazard of about 53%, which is sustained thereafter. Similarly, patients in the lenvatinib arm experience a reduction of progression hazard of about 47% at 529 days. As before, the estimated mean lifetime PFS for these patient groups was estimated as the sum of the AUC in each trial arm, followed by lifetime extrapolation using the long-term exponential hazard of progression or death. This approach yields estimates of mean lifetime PFS of 41.00 months for patients receiving lenvatinib and 6.92 months for patients in the placebo arm of SELECT. Thus, the estimated net lifetime gain in PFS for patients receiving lenvatinib is estimated to be 34.08 months.

Time to treatment discontinuation

As illustrated in *Figure 13*, the SELECT data are virtually complete for the cycles of lenvatinib dispensed during the trial. The AG estimates mean usage of lenvatinib as 12.61 30-day cycles per patient.

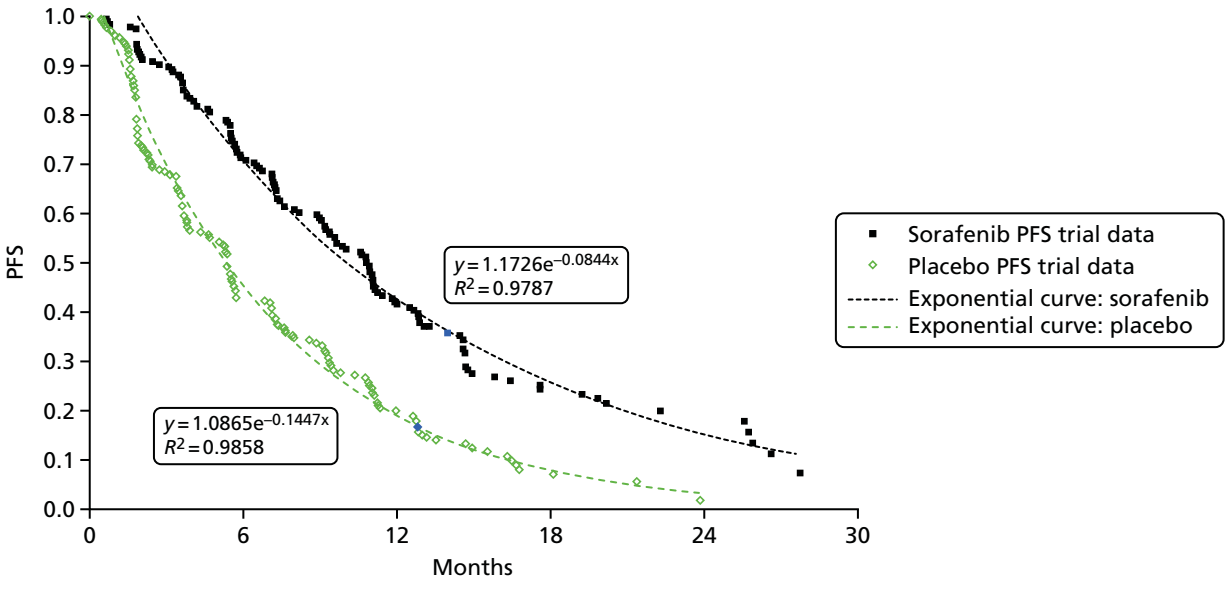

FIGURE 11 Progression-free survival K–M data from DECISION modelled by an exponential function.

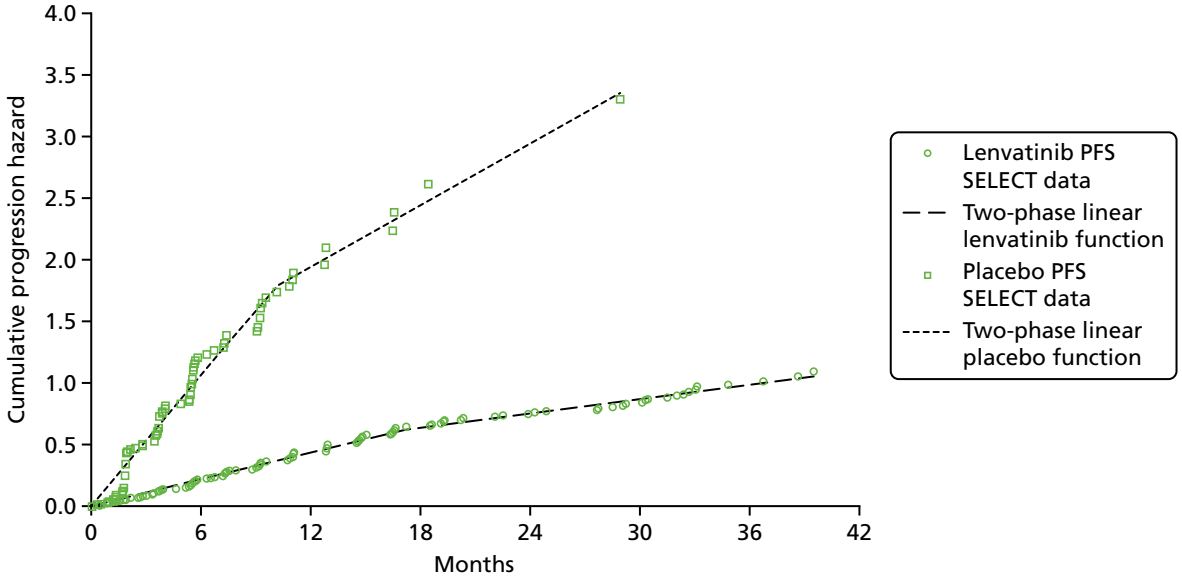

FIGURE 12 Cumulative hazard for disease progression for SELECT, with two-phase fitted exponential models.

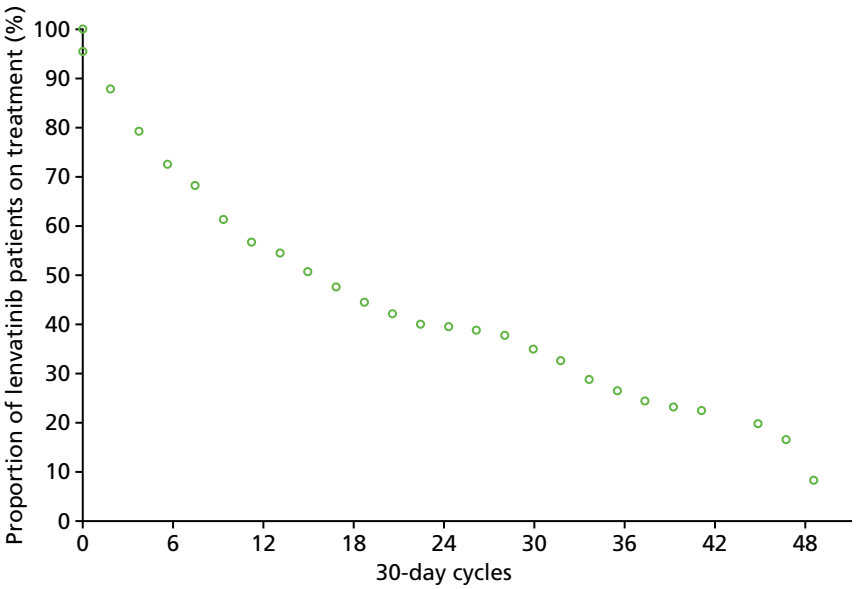

FIGURE 13 The 30-day cycles of lenvatinib dispensed in SELECT.

The DECISION trial data are also complete for the cycles of sorafenib dispensed during the trial, as illustrated in *Figure 14*. The AG estimates mean usage of sorafenib as 14.36 28-day cycles per patient.

Overall survival

Data provided by the company for lenvatinib-treated patients in SELECT (*Figure 15*) show a simple long-term exponential trend indicating a constant mortality risk throughout the trial period (19.6% per year). This allows the mean lifetime OS for patients treated with lenvatinib to be estimated using the AUC of the trial K–M curve until 34.7 months plus a simple exponential extrapolation thereafter, giving a total mean OS of 55.1 months.

Both companies have employed RPSFTM adjustments to data from the placebo arms of their clinical trials to correct for patients crossing over to the active treatment following disease progression. Adjusted OS placebo arm data from SELECT are also displayed in *Figure 15* and indicate that, after RPSFTM adjustment,

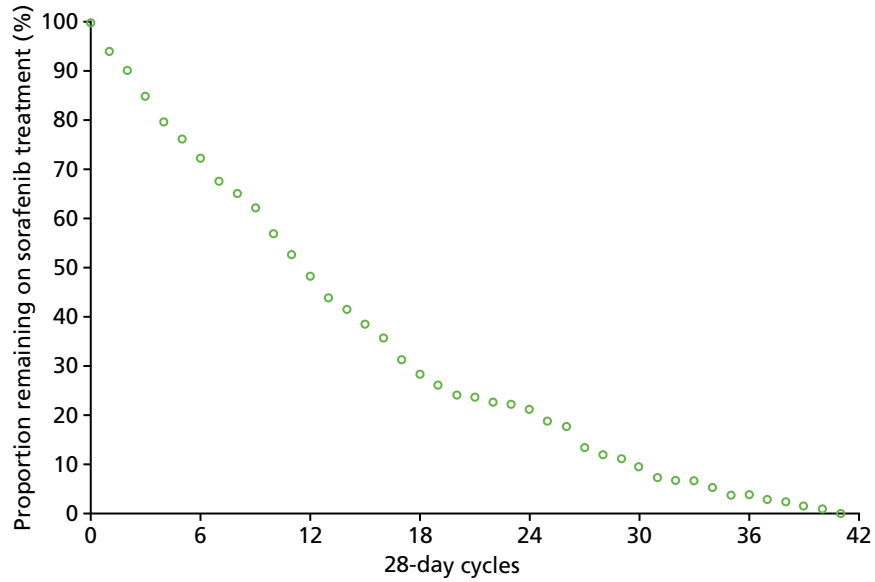

FIGURE 14 The 28-day cycles of sorafenib dispensed in DECISION.

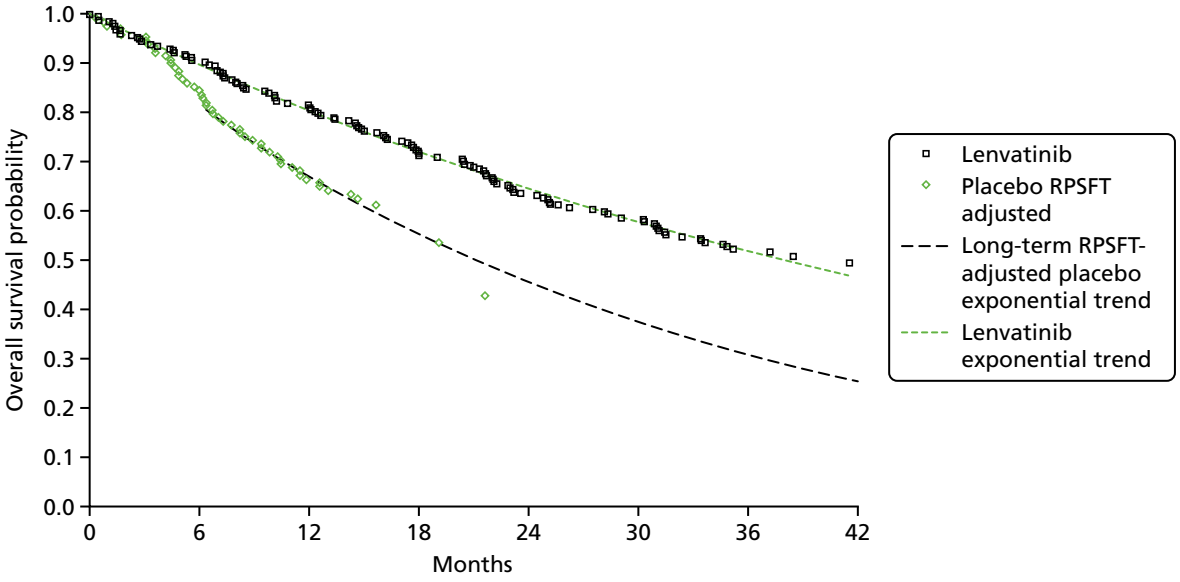

FIGURE 15 Overall survival: lenvatinib-treated patients in SELECT with a fitted exponential model, and RPSFTM adjusted for placebo patient crossover with a long-term exponential-fitted model.

a similar long-term exponential (constant risk) trend also applies to the placebo arm beyond 6 months. Using the AUC of the adjusted K–M curve until 19.1 months plus the exponential extrapolation thereafter yields a lifetime estimated mean OS for the corrected placebo arm of 29.9 months and a net estimated OS gain attributable to treatment with lenvatinib of 25.3 months.

An examination of the OS data from DECISION (*Figure 16*) indicates that both patients in both treatment arms were subject to a period of relatively low mortality hazard, followed by transition to a higher constant risk of death. This transition took place after 11.2 months for sorafenib patients and 6.4 months for placebo patients.

Using the AUC of the RPSFTM-adjusted K–M curve for the placebo arm until 6.4 months plus the AUC of the exponential extrapolation thereafter yields a lifetime estimated mean OS for the placebo arm

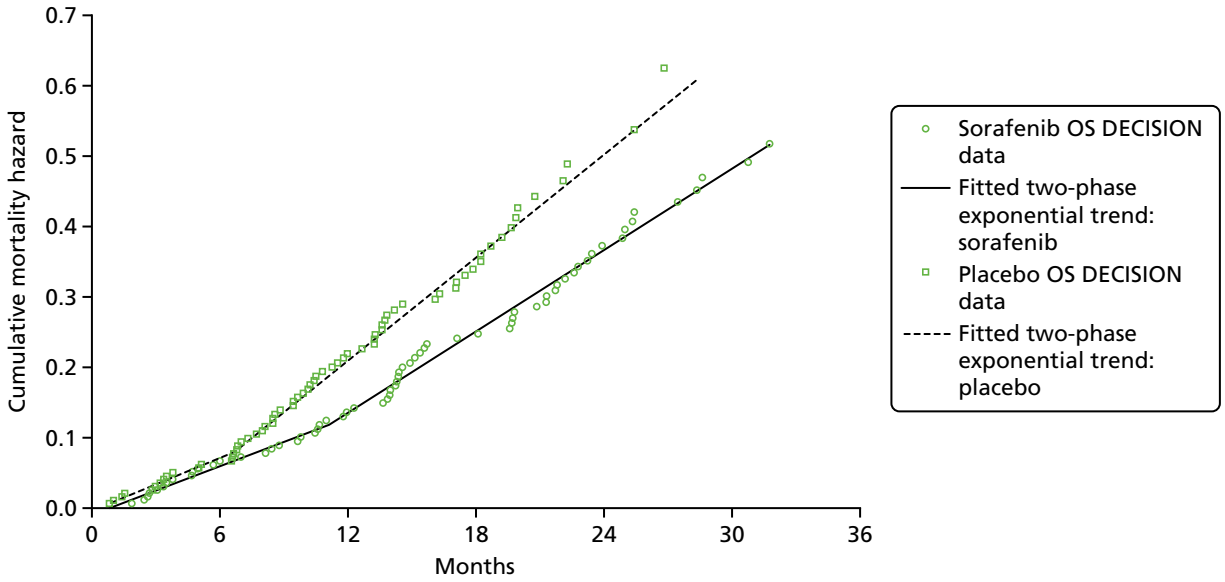

FIGURE 16 Cumulative mortality hazard for sorafenib-treated patients in DECISION with a fitted two-phase exponential model, and for RPSFTM-adjusted placebo patients with a fitted two-phase exponential model.

of 47.18 months. Similarly, combining the AUC of the sorafenib arm up to 11.96 months with the exponential trend thereafter yields an estimated lifetime mean OS of 56.66 months. Thus, the net mean OS gain attributable to sorafenib is 9.48 months.

Postprogression survival

Assessment of PPS may be carried out at an aggregate level by calculating the difference between model estimates of OS and PFS. However, it can also be informative to consider this outcome at the level of individual patients, at which it may provide useful insight into possible post-treatment long-term effects of treatments even after active treatment has ceased. The AG asked both companies to provide PPS data from their respective primary clinical trials. Unfortunately, only data from SELECT have been received. As with OS, it is important to allow for the effects of crossover on PPS by using RPSFTM-adjusted data.

In *Figure 17*, the beneficial effect of crossover to lenvatinib for patients initially randomised to the placebo arm is clearly apparent. Both trial arms exhibit a similar early pattern, albeit at different absolute levels of survival, and thereafter show similar long-term exponential trends after 15 to 18 months from the time of disease progression. When the RPSFTM adjustment is applied, the corrected placebo arm very closely follows the trajectory of the lenvatinib arm (although the effect of RPSFTM revised censoring does not allow direct comparison beyond 16 months). Nonetheless, these data suggest that, after crossover adjustment, there is probably no additional benefit to individual patients crossing from placebo to lenvatinib beyond what would have been gained by treatment prior to disease progression.

Summary of time-to-event outcome data analysis

Estimates of PFS, OS and PPS and mean cycles of active treatment received in the two clinical trials are displayed in *Table 22*. The main difference occurs in the PFS results in which lenvatinib provides substantially greater benefit than sorafenib (34.1 additional months before progression compared with only 6.3 months, respectively). However, the estimated OS results are very similar (55.1 for lenvatinib vs. 56.8 months for sorafenib), and, consequently, estimated PPS is reduced with lenvatinib treatment but increased for sorafenib treatment). Thus, it appears that lenvatinib shows effect more strongly in initially delaying progression, but does not offer additional benefit over sorafenib in terms of long-term survival. The duration of active treatment in the two trials is very similar when measured in days rather than cycles, with a difference of < 7%.

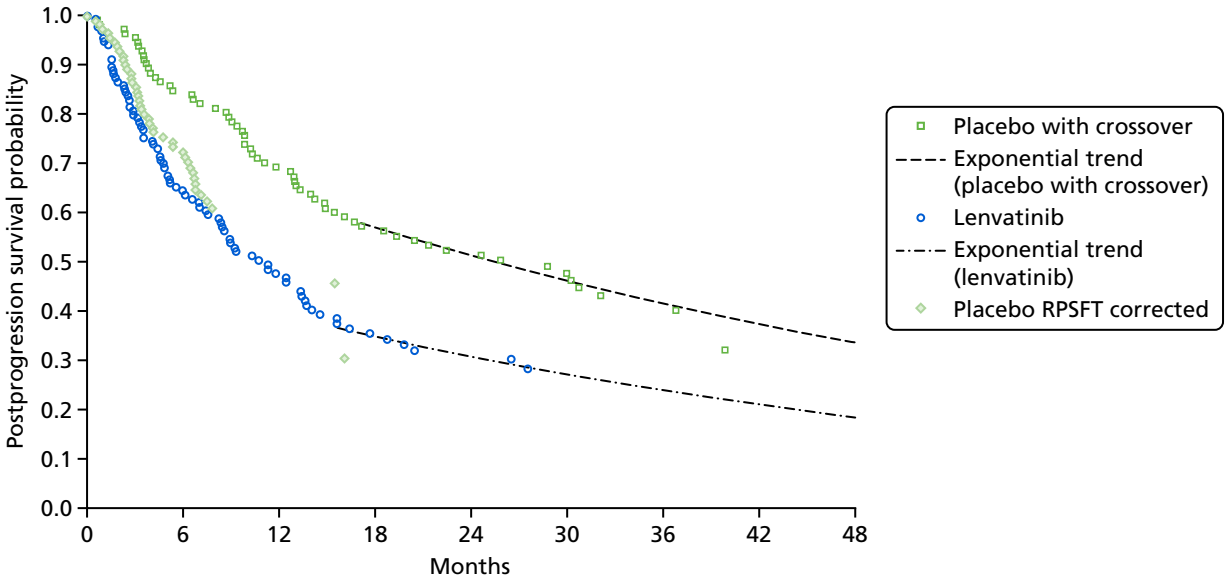

FIGURE 17 Postprogression survival: lenvatinib in SELECT with a fitted exponential model, and RPSFTM adjusted for placebo patient crossover with a long-term exponential-fitted model.

TABLE 22 The AG estimated mean time-to-event outcome variables

Study, treatment arm	PFS (months)	OS (months)	PPS (months)	TTD (cycles)
SELECT				
Lenvatinib	41.0	55.1	14.1	12.6 (30-day cycle)
Placebo	6.9	30.2[a]	23.3	N/A
Change attributable to lenvatinib	+ 34.1	+ 24.9	–9.2	N/A
DECISION				
Sorafenib	13.8	56.8	42.9	14.4 (28-day cycle)
Placebo	7.6	43.8[a]	36.2	N/A
Change attributable to sorafenib	+ 6.3	+ 13.0	+ 6.7	N/A

N/A, not applicable; TTD, time to treatment discontinuation.
a RPSFTM adjusted for crossover in placebo arms.

Health-related utility data

The AG has carefully considered the opposing approaches used by the two companies to estimate appropriate health-related utility values to assign to health states and to AEs. The Eisai Ltd model relies heavily on the Fordham *et al.*[168] vignette study (which it sponsored), whereas the Bayer HealthCare model draws on EQ-5D-3L data collected during DECISION.

On theoretical grounds, directly collected evidence from patients with the condition (as used in the Bayer HealthCare model[7]) should always be preferred to the results of an artificial study without recourse to the views of patients either in design or calibration (as used in the Eisai Ltd model). Of particular concern is the serious overestimation of baseline utility values in the Fordham *et al.*[168] study when compared with UK general population values for people of a similar age. The contrary position argues that DECISION data include the disutility of AEs in estimates of health-state utilities, and, therefore, are biased without any objective means of adjusting the health-state estimates.

On balance, the AG considers that the data from DECISION should be used in the base case (*Table 23*) with a sensitivity analysis using the Eisai Ltd model values.

TABLE 23 The AG-preferred health-related utility values

Health state	Treatment arm	Base-case utility value	SE	Sensitivity analysis utility value	SE
PFS	Lenvatinib/sorafenib	0.72	0.08	0.76/0.68	0.08
PFS	BSC	0.80	0.07	0.80	0.019
PPS	All	0.64	0.06	0.50	0.028

SE, standard error.

Resource use and cost data used in the Assessment Group's model

Active treatments (lenvatinib and sorafenib)

The lenvatinib full acquisition cost is £4311.00 per 30-day treatment (NHS Indicative Price, BNF June 2017).[47] This is reduced by the SELECT dose intensity factor (72.5%) so the true cost per cycle is £3089.55.

The sorafenib full acquisition cost is £3576.56 per 28-day treatment (NHS Indicative Price, BNF June 2017).[47] This is reduced by the DECISION dose intensity factor (81.40%) so the true cost per cycle is £2911.32.

There is no administration cost associated with either drug, both of which can be safely taken unsupervised. The NHS Reference Costs[174,175] figures quoted by both companies for administration of oral treatment relate to particular drugs that may cause serious rapid-onset reactions, and so the patient must be monitored following administration. Thus, it is not appropriate to use these costs when estimating the cost of either sorafenib or lenvatinib.

Routine care costs

Table 24 summarises the schedule of itemised routine care tests, treatments and specialist visits identified by the AG's clinical advisor, in terms of use per quarter (3 months), per 28-day cycle and per 30-day cycle. These items are considered to be applicable to all patients.

Adverse events

Three common AEs feature in the two company models for which treatment types and resource use were estimated by the AG's clinical advisor. The cost estimates shown in *Table 25* are for only a single cycle (28 days or 30 days) and take no account of AE episodes that do not resolve within that time or that subsequently recur.

End-of-life care

Health-care costs during the last 90 days of life were estimated using the results presented in Table 9 of the paper by Georghiou and Bardsley;[173] costs were uplifted from 2010/11 to 2015/16 using the Hospital and Community Heath Services inflation index[178] as shown in *Table 26*.

Cost-effectiveness results

Deterministic cost–utility results from the AG model using public list prices are compared with submitted results from the two companies in *Tables 27* (vs. the Eisai Ltd model) and *28* (vs. the Bayer HealthCare model). Overall, the estimates of incremental costs from the three models are not very different, but estimates of outcomes (life-years and QALYs) show larger discrepancies across the models, reflecting the different assumptions and estimation methods employed. The ICERs per QALY gained reported from the AG model are substantially greater than those obtained from the Bayer HealthCare model, but the Eisai Ltd's model results show a much larger ICER per QALY gained for sorafenib versus BSC than that obtained from either of the other models.

Inevitably, the relative economic performance of the treatments in all three models will change significantly when final discounted acquisition prices are applied.

TABLE 24 The AG-estimated mean routine care resource use and cost per patient

Resource item	Number per quarter	Unit cost (£)	SE (£)	Reference cost (source: *NHS Reference Costs 2015 to 2016*[174])
Blood test	1	3.10	0.07	NHS Reference Cost DAPS05
Coagulation test	1	3.10	0.07	NHS Reference Cost DAPS05
Urine test	1	7.63	0.22	NHS Reference Cost DAPS07
Liver function test	7	1.18	0.03	NHS Reference Cost DAPS04
Thyroid function test	3	1.18	0.03	NHS Reference Cost DAPS04
Protein test	1	1.18	0.03	NHS Reference Cost DAPS04
Bone scan	1	242.39	7.56	NHS Reference Cost NMOP/RN15A
MRI scan	1	204.67	5.07	NHS Reference Cost IMAGOP/RD03Z
CT scan	1	118.53	2.92	NHS Reference Cost IMAGOP/RD22Z
Thyroxine (4-weekly)	3.26	4.04	NS	BNF NHS indicative prices
Calcium and vitamin D	3	7.13	NS	BNF NHS indicative prices
Specialist oncology visit	1	162.84	4.37	NHS Reference Cost 370/WF01A
Total per 3 months		789.81		
Total per 28-day cycle		242.19		
Total per 30-day cycle		259.48		

NS, not stated; SE, standard error.

TABLE 25 The AG-estimated AE resource use and treatment costs

			Incidence rate (%)			
AE	Resource item	Unit cost (£)	Sorafenib	Lenvatinib	Placebo vs. sorafenib	Placebo vs. lenvatinib
Hand–foot syndrome	Diprobase 500-g pump pack	10.00 (typical retail price)	20.29	3.45	0.00	0.00
Proteinuria	2.5 mg of Ramipril × 28	0.27 (eMIT, April 2016[179])	0.00	3.45	0.00	0.00
Hypertension	10 mg of Amlodipine × 28	0.19 (eMIT, April 2016[179])	0.00	42.91	1.91	3.82
	10 mg of Ramipril × 28	0.41 (eMIT, April 2016[179])	0.00	42.91	1.91	3.82
	Two extra oncology consultations	162.84 per visit (*NHS Reference Costs 2015 to 2016*[174])	0.00	42.91	1.91	3.82
Total cost (£)						
Per 28 days			33.55	140.37	6.24	12.45
Per 30 days			35.95	150.40	6.69	13.34

eMIT, electronic market information tool.

TABLE 26 The AG-estimated end-of-life (final 90 days) resource use and treatment costs

Care item	Mean cost per patient (£)	SE (£)
GP consultation	391.78	4.98
District nursing	631.14	53.77
Local authority social care	476.57	11.28
Emergency inpatient episode	4369.67	6.28
Non-emergency inpatient episode	1459.78	5.06
Outpatient attendance	405.73	1.10
Accident and emergency visit	85.87	0.15
Total	7820.54	

GP, general practitioner; SE, standard error.

TABLE 27 Cost-effectiveness estimated results comparing the AG's model and Eisai Ltd's model using published list prices[47]

	AG's model preferred scenario						
	Lenvatinib vs. BSC		Sorafenib vs. BSC		Eisai Ltd's model estimates		
Results component	Lenvatinib	BSC	Sorafenib	BSC	Lenvatinib	Sorafenib	BSC
Costs (£)							
Drug acquisition	68,217	0	41,281	0	68,061[b]	37,267	0
Drug administration	0	0	0	0	0	0	0
Routine care	12,742	7495	13,227	10,523	31,022	38,937	35,582
AEs	7385	385	1833	274	107	21	0
End-of-life care	6758	7314	6848	7157	6316	6615	6532
Total	95,102	15,195	63,188	17,954	107,182	82,839	42,115
Life-years							
Response (in PFS) years[a]	N/A	N/A	N/A	N/A	0.533	0.325	0.017
Progression-free years[a]	3.413	0.565	1.064	0.635	3.062	0.922	0.640
Postprogression years[a]	1.171	1.967	3.661	3.014	1.277	2.258	2.159
Total[a]	4.584	2.532	4.725	3.649	4.339	3.180	2.800
QALYs							
PFS	2.182	0.446	0.755	0.504	2.380	0.746	0.447
PPS	0.633	1.156	1.997	1.720	0.800	1.351	1.393
Total	2.815	1.602	2.752	2.224	3.179	2.097	1.840
Incremental cost (£)	79,907		45,234		65,067	40,724	N/A
Incremental life-years	2.052		1.076		1.539	0.380	N/A
Incremental QALYs	1.213		0.528		1.339	0.257	N/A
ICER per QALY vs. BSC (£)	65,872		85,644		48,569	158,232	N/A

N/A, not applicable.
a Life-years undiscounted.
b AG-corrected half-cycle error.
Note
The AG drug costs are at list prices (no discounts).

TABLE 28 Cost-effectiveness estimated results comparing the AG's model and the Bayer HealthCare model using published list prices[47]

	AG-preferred scenario						
	Lenvatinib vs. BSC		Sorafenib vs. BSC		Bayer HealthCare model estimates		
Results component	Lenvatinib	BSC	Sorafenib	BSC	Lenvatinib	Sorafenib	BSC
Costs (£)							
Drug acquisition	68,217	0	41,281	0	41,641	33,187	0
Drug administration	0	0	0	0	0	0	0
Routine care	12,742	7495	13,227	10,523	46,018	37,886	25,695
AEs	7385	385	1833	274	141	81	17
End-of-life care	6758	7314	6848	7157	0	0	0
Total	95,102	15,195	63,188	17,954	87,800	71,154	25,712
Life-years							
Response years	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Progression-free years	3.413	0.565	1.064	0.635	3.767	1.342	0.808
Postprogression years	1.171	1.967	3.661	3.014	3.589	4.381	3.161
Total life-years[a]	4.584	2.532	4.725	3.649	7.356	5.723	3.969
QALYs							
PFS	2.182	0.446	0.755	0.504	2.394	0.920	0.628
PPS	0.633	1.156	1.997	1.720	1.645	2.237	1.724
Total	2.815	1.602	2.752	2.224	4.039	3.158	2.352
Incremental cost (£)	79,907		45,234		62,088	45,441	62,088
Incremental life-years[a]	2.052		1.076		3.487	1.754	3.487
Incremental QALYs	1.213		0.528		1.687	0.805	1.687
ICER (per QALY) (£)	65,872		85,644		36,802	56,417	36,802

N/A, not applicable.
a Life-years undiscounted.
Note
The AG drug costs are at list prices (no discounts).

Structural sensitivity analysis

The AG cross-trial ICERs per QALY gained can be readily calculated by interchanging the results shown in the two AG BSC columns of *Tables 27* and *28*. For sorafenib, this results in an incremental cost per patient of £47,993 and incremental QALYs per patient of 1.150, leading to an exploratory ICER of £41,716 per QALY gained. However, for lenvatinib, the incremental cost per patient is £77,148 and the incremental QALYs per patient are 0.591, leading to an amended ICER of £130,592 per QALY gained.

These very large changes (an increase of 105% in the lenvatinib ICER per QALY gained, and a decrease of 54% in the sorafenib ICER per QALY gained) serve to illustrate that the choice of BSC comparator is of major importance in this appraisal, and that the absence of credible indirect comparison results precludes any simple resolution of this difficulty.

Deterministic sensitivity analyses

Sensitivity analyses have been conducted on the cost-effectiveness results obtained using the AG model and the results from these analyses are shown in *Tables 29–31*.

TABLE 29 Effects of non-stochastic uncertainty on estimated ICER per QALY gained

Treatment	Source of uncertainty	AG-preferred scenario: cost per QALY gained (£)	Option A		Option B	
			Cost per QALY gained (£)	Effect on ICER per QALY gained (£)	Cost per QALY gained (£)	Effect on ICER per QALY gained (£)
Lenvatinib vs. BSC	Discount rate – costs: A = 0%, B = 5%	65,872	70,033	4161	64,368	–1504
	Discount rate – outcomes: A = 0%, B = 5%	**65,872**	**53,592**	**–12,280**	**71,274**	**+5402**
	Drug use data source: A = PFS, B = least of TTD and PFS	**65,872**	**106,178**	**+40,306**	**65,872**	**0**
	Drug dose intensity ratio: A = not used	**65,872**	**87,203**	**+21,331**	N/A	N/A
	Utility value set: A = Eisai Ltd	**65,872**	**54,981**	**–10,891**	N/A	N/A
Sorafenib vs. BSC	Discount rate – costs: A = 0%, B = 5%	85,644	88,747	+3104	84,561	–1082
	Discount rate – outcomes: A = 0%, B = 5%	**85,644**	**67,645**	**–17,999**	**93,751**	**+8108**
	Drug use data source: A = PFS, B least of TTD and PFS	85,644	85,814	+170	83,076	–2568
	Drug dose intensity ratio: A = not used	**85,644**	**103,503**	**+17,859**	N/A	N/A
	Utility value set: A = Eisai Ltd	**85,644**	**105,666**	**+20,023**		

N/A, not applicable; TTD, time to treatment discontinuation.

Note

Bold text denotes variables modifying the estimated value by > £5000 per QALY gained.

TABLE 30 Effects of stochastic uncertainty on estimated lenvatinib vs. BSC (ICER per QALY gained)

Source of uncertainty	AG-preferred scenario: cost per QALY gained (£)	LCL		UCL	
		Cost per QALY gained (£)	Effect on ICER per QALY gained (£)	Cost per QALY gained (£)	Effect on ICER per QALY gained (£)
Dose intensity ratio	65,872	63,892	–1980	67,852	+1980
Blood/coagulation test cost	65,872	65,871	–2	65,874	+2
Urine test cost	65,872	65,871	–1	65,876	+4
Liver/thyroid/protein test cost	65,872	65,870	–2	65,877	+5
Bone scan cost	65,872	65,792	–80	65,955	+83
CT scan cost	65,872	65,842	–30	65,905	+33
MRI scan cost	65,872	65,819	–53	65,928	+56
Oncology visit cost	65,872	65,524	–348	66,223	+351
Hand–foot syndrome incidence: lenvatinib	65,872	65,866	–6	65,888	+15
Proteinuria incidence: lenvatinib	65,872	65,873	+1	65,874	+2
Hypertension incidence: lenvatinib	65,872	65,018	–854	66,759	+887
Hypertension incidence: BSC (vs. lenvatinib)	65,872	66,074	+202	65,431	–441
End-of-life care costs	65,872	65,883	+11	65,864	–8
PFS utility values	**65,872**	**77,475**	**+11,603**	**42,352**	**–23,520**
PPS utility values	**65,872**	**60,739**	**–5133**	**71,956**	**+6084**
PFS lenvatinib hazard rate	65,872	63,127	–2745	63,853	–2019
PFS BSC hazard rate (SELECT)	65,872	63,672	–2200	63,389	–2483
OS lenvatinib hazard rate	65,872	63,231	–2641	63,791	–2081
OS BSC hazard rate (SELECT)	65,872	68,374	+2502	65,455	–417
TTD lenvatinib hazard rate	65,872	65,006	–866	63,201	–2671

LCL, lower confidence limit; TTD, time to treatment discontinuation; UCL, upper confidence limit.

Note

Bold text denotes variables modifying the estimated value by > £5000 per QALY gained.

TABLE 31 Effects of stochastic uncertainty on estimated sorafenib vs. BSC (ICER per QALY gained)

Source of uncertainty	AG-preferred scenario: cost per QALY gained (£)	LCL		UCL	
		Cost per QALY gained (£)	Effect on ICER per QALY gained (£)	Cost per QALY gained (£)	Effect on ICER per QALY gained (£)
Dose intensity ratio	85,644	83,009	–2635	88,278	+2635
Blood/coagulation test cost	85,644	85,642	–2	85,645	+2
Urine test cost	85,644	85,643	–1	85,648	+5
Liver/thyroid/protein test cost	85,644	85,641	–2	85,649	+6
Bone scan cost	85,644	85,549	–94	85,741	+98
CT scan cost	85,644	85,608	–35	85,682	+39
MRI scan cost	85,644	85,581	–63	85,710	+66
Oncology visit cost	85,644	85,446	–198	85,845	+201
Hand–foot syndrome incidence: sorafenib	85,644	85,592	–51	85,710	+66
Hypertension incidence: sorafenib	85,644	84,460	–1184	87,356	+1712
Hypertension incidence: BSC (vs. sorafenib)	85,644	85,999	+355	84,782	–862
End-of-life care costs	85,644	85,657	+14	85,633	–10
PFS utility values	**85,644**	**97,212**	**+11,568**	**59,422**	**–26,221**
PPS utility values	**85,644**	**95,450**	**+9806**	**77,668**	**–7976**
PFS sorafenib hazard rate	85,644	85,294	–349	85,367	–277
PFS BSC hazard rate (DECISION)	85,644	85,298	–346	85,383	–261
OS sorafenib hazard rate	**85,644**	**78,853**	**–6790**	**92,528**	**+6884**
OS BSC hazard rate (DECISION)	85,644	89,074	+3430	82,063	–3581

LCL, lower confidence limit; TTD, time to treatment discontinuation; UCL, upper confidence limit.
Note
Bold text denotes variables modifying the estimated value by > £5000 per QALY gained.

The AG identified five modelling issues, which do not involve stochastic uncertainty, and the implications, in terms of changes to the size of the estimated ICER per QALY gained in the AG model, that result from changes to these parameter values are shown in *Table 29*. Assuming that a change in the estimated ICER per QALY gained of < £5000 is not considered substantial, all but one of the five issues generated important changes in the ICER per QALY gained estimates for either sorafenib or lenvatinib (the exception being the discount rate applied to costs).

The AG identified 18 parameter values for which stochastic uncertainty could be quantified in the AG model, and the findings from adjusting these values are summarised in *Tables 30* and *31*. Only three parameters (the utility values for the PFS and PPS health states estimated from EQ-5D-3L patient data in DECISION, and the sorafenib OS AG extrapolation hazard) were found to lead to substantial effects on the

size of the estimated ICER per QALY gained when varied between the lower and upper 95% confidence limits. In particular, the AG considers that uncertainty in specific unit costs (other than drug acquisition costs) is not an important factor when generating uncertainty in ICER per QALY gained estimates.

Probabilistic sensitivity analyses

The AG carried out PSA varying model parameters subject to quantifiable stochastic sampling uncertainty:

- nine routine care cost variables
- seven AE incidence rates
- seven health-related utility values
- seven end-of-life health and social care costs.

In most cases, probabilistic values were drawn from normal distributions around the standard error of the mean, except for incidence rates, for which beta distributions were employed.

Using list prices, the in-trial comparisons of lenvatinib and BSC (*Figure 18*) and of sorafenib and BSC (*Figure 19*) yielded similar deterministic and probabilistic ICERs per QALY gained.

Unfortunately, information relating to the key outcome variables (PFS, OS and time to treatment discontinuation) provided to the AG by one of the companies was not in the form requested, and information on uncertainty in the estimated treatment dose intensity was not included by the other company in its submission or their model. Without these key data items, it was not possible to incorporate these important components of the normal PSA on this occasion. Therefore, the results presented below should be treated with caution.

For the comparison of lenvatinib with BSC, the deterministic ICER is £65,872 per QALY gained and the probabilistic ICER is £66,038 per QALY gained.

For the comparison of sorafenib with BSC, the deterministic ICER is £85,644 per QALY gained and the probabilistic ICER is £83,547 per QALY gained.

The variation in additional cost per patient is much smaller relative to the uncertainty in outcomes (QALYs) gained because of the dominance of drug acquisition costs, which constitute 85–90% of the incremental cost per patient when full list prices are assumed to apply.

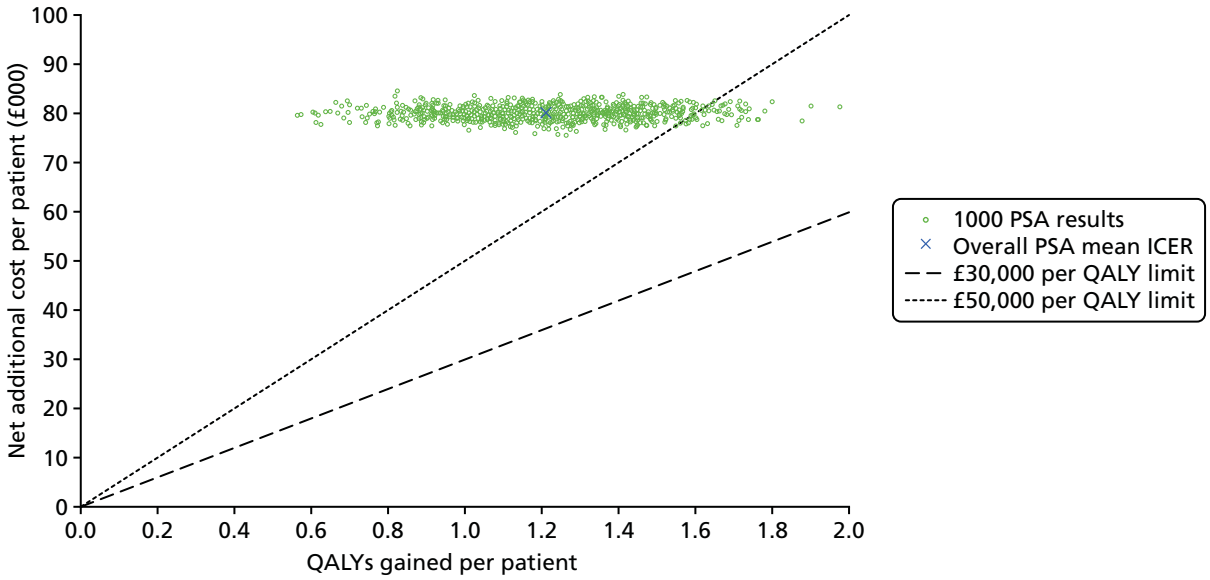

FIGURE 18 Probabilistic sensitivity analysis: lenvatinib vs. BSC in SELECT.

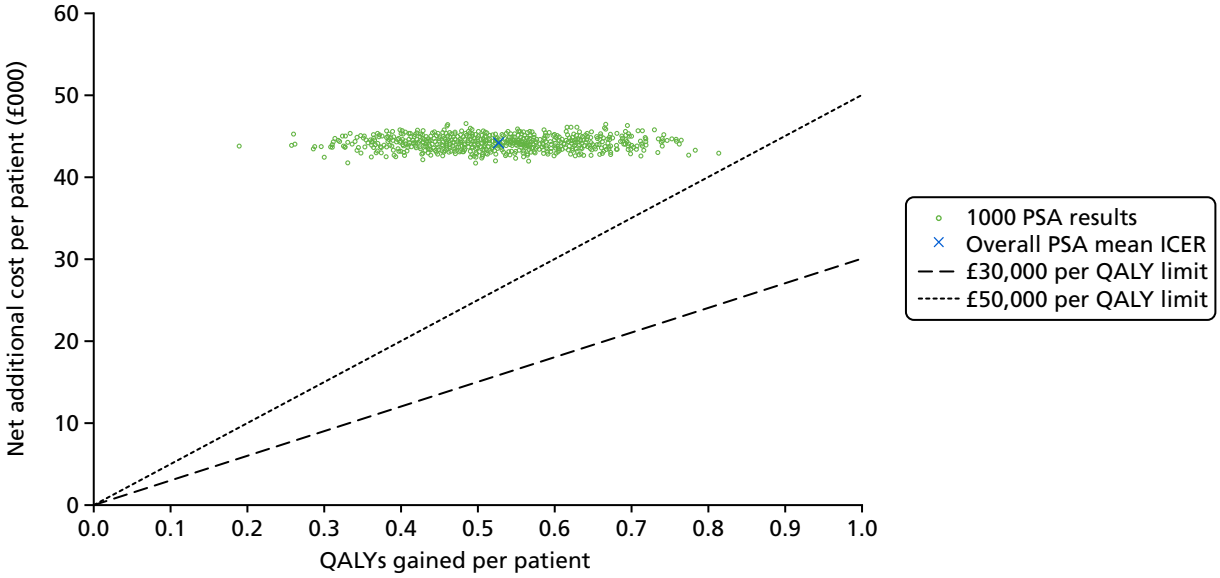

FIGURE 19 Probabilistic sensitivity analysis: sorafenib vs. BSC in DECISION.

Clearly, both treatments exhibit estimated ICERs well above £50,000 per QALY gained if list prices are applied. This is confirmed by the cost-effectiveness acceptability curves (CEACs) presented in *Figures 20* and *21*. An examination of the CEACs shows that, compared with BSC, the probability of sorafenib being cost-effective at a threshold of £50,000 per QALY gained is < 0.05% and the probability of lenvatinib being cost-effective is 5.4%.

Discussion and summary of cost-effectiveness results

The comparison of data from the placebo arms of SELECT and DECISION indicated that the experience of patients differed markedly for PFS, the principal outcome of both trials, to the extent that the PHs assumption is violated. This invalidates the derivation and application of HRs in order to model an indirect comparison to compare the effectiveness of lenvatinib with that of sorafenib. As a consequence, the AG was only able to carry out separate economic assessments of each active treatment against its trial comparator, using common methods and shared parameter values.

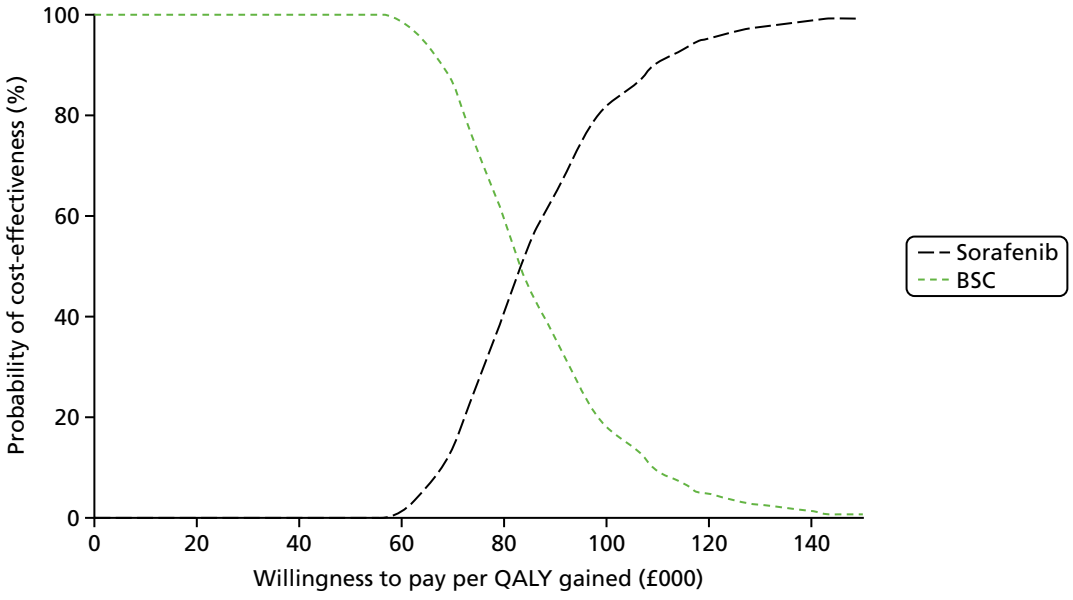

FIGURE 20 Cost-effectiveness acceptability curves for sorafenib vs. BSC (DECISION).

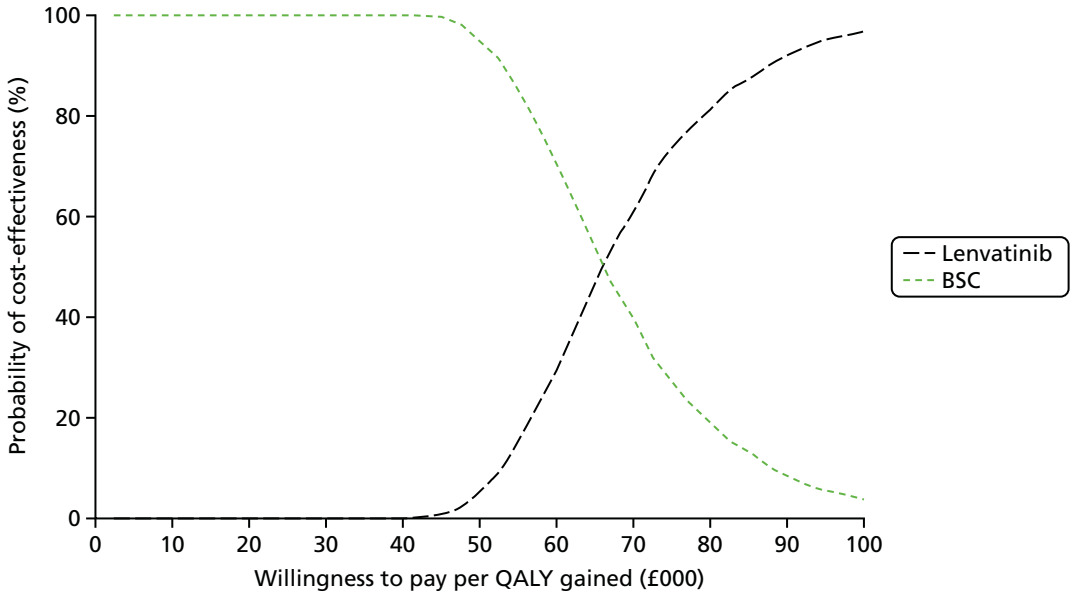

FIGURE 21 Cost-effectiveness acceptability curves for lenvatinib vs. BSC (SELECT).

In order to assess the importance of the available placebo data (used to represent long-term BSC), a structural sensitivity analysis was carried out substituting the placebo arm data from each trial as the comparator for the intervention treatment. These analyses resulted in very large changes to the AG's estimated base-case ICERs per QALY gained, and confirmed the suspicion that the two trial populations are not equivalent.

Using published list prices[47] in the AG model, neither treatment was found to be cost-effective at a willingness-to-pay threshold of £50,000 per QALY gained. Moreover, neither treatment meets the NICE end-of-life criteria for special consideration [the AG analyses show that both are indicated to have a lifetime mean estimated OS of 55 to 57 months, and a survival gain versus standard of care (BSC/placebo) of > 9 months].

A comparison of the patterns of clinical effectiveness of the two treatments suggests that the proportion of the average gain in PFS, which is subsequently translated to a gain in OS, is very different between the treatments (73% for lenvatinib vs. 24% for sorafenib). This suggests quite different modes of action, which may have important consequences for patients' long-term prognoses.

The estimated mean time spent in the PFS and OS health states in the AG model show little difference between the two active treatments, so that apparently different net outcome gains are mainly attributable to large differences in the experience of patients in the comparator arms of the two trials. This consistency of outcomes for the active treatments, and the apparently different modes of action, may suggest that these treatments could be used sequentially to generate additional long-term benefit.

Assessment of factors relevant to the NHS and other parties

Lenvatinib and sorafenib are both MKIs and have been approved for use for treating RR-DTC in NHS Scotland (contingent on the continuing availability of PAS prices). Sorafenib is currently available in NHS England via the CDF. Therefore, it is not anticipated that, if recommended by NICE, the use of lenvatinib and sorafenib would have major implications for NHS service provision, particularly as the administration and AEs from both therapies are broadly in line with those of other TKIs already used to treat patients with cancer in the NHS.

Chapter 6 Discussion

Statement of principal findings

Clinical effectiveness results

The main sources of clinical effectiveness evidence were two good-quality RCTs (SELECT[51] and DECISION[52]). Results from these trials show that treatment with either lenvatinib or sorafenib statistically significantly improves median PFS and ORR when compared with placebo. Median OS results demonstrate that there is no statistically significant difference in effect when treatment with lenvatinib or sorafenib are compared with placebo. Treatment crossover confounds the OS results from both trials and, to adjust for this effect, OS data were modified using RPSFTM. The results from the adjusted analyses show that, when compared with placebo, treatment with lenvatinib statistically significantly improves OS but there is still no statistically significant improvement in OS from treatment with sorafenib. However, the AG considers that the assumption of PH for unadjusted OS, adjusted OS and PFS is violated in SELECT and is violated for adjusted OS and PFS in DECISION; therefore, these results should be interpreted with caution. Nonetheless, clinical advice to the AG is that the improvements in PFS and the benefits from active treatment do appear to be clinically meaningful.

The AG considers that the improvements in OS and PFS for patients treated with lenvatinib and sorafenib when compared with placebo are likely to reflect improvements in OS and PFS when compared with BSC, notwithstanding the possible differences in the BSC received by the patients in the two trials.

The AG highlights that differences exist between the median OS and PFS results from the observational studies,[59,77,78,81,88,101,103,126,135,137] and those from SELECT and DECISION: OS for patients treated with lenvatinib and sorafenib in SELECT and DECISION was longer than the OS reported in the observational studies. In contrast, in DECISION, PFS for patients treated with sorafenib was shorter than for in any of the prospective observational studies and the two meta-analyses.[127,138] Median PFS for patients treated with lenvatinib in SELECT was longer than suggested by the prospective, observational results from Study 201[77] and shorter than in Study 208.[135]

Results from indirect comparisons and MAICs[7,8,57,97] show that treatment with lenvatinib leads to better PFS (but not OS) than treatment with sorafenib. The AG did not conduct an indirect comparison as preliminary analyses suggested that using data from SELECT and DECISION in the same network would generate unreliable results. The AG's preliminary analyses showed that the PFS risk profiles (as demonstrated by a comparison of K–M data) of the SELECT and DECISION populations receiving placebo were not comparable. In addition, results from the AG's analyses showed that, within SELECT and DECISION, the PH assumption did not hold for the majority of survival outcomes. For data to be included in a network, the assumption of PH should hold both across trials and within trials. The AG's analyses have demonstrated that this assumption is often violated. As a consequence of this violation, the AG has been unable to compare lenvatinib with sorafenib. The AG considers that the relative clinical effectiveness of these two drugs cannot currently be reliably determined.

As expected, both treatment with lenvatinib and with sorafenib resulted in more AEs than treatment with placebo. Both all-grade and grade ≥ 3 diarrhoea were common for patients treated with lenvatinib and those treated with sorafenib. However, the most common AE experienced by patients treated with lenvatinib was hypertension and the most common AE experienced by patients treated with sorafenib was hand–foot syndrome. Dose reductions were frequent for patients treated with lenvatinib (67.8%) and for patients treated with sorafenib (64.3%). The results of published indirect comparisons[97] suggest that when treatment with sorafenib is compared with lenvatinib, the incidence of alopecia is higher but the incidence of hypertension is reduced, and those treated with sorafenib experience fewer grade ≥ 3 AEs, SAEs and withdrawals owing to AEs.

The impact of treatment with lenvatinib on HRQoL was not assessed in SELECT and is, therefore, unknown; this is a limitation of the trial given the difference in the safety profiles for some of the AEs associated with lenvatinib and sorafenib. Sorafenib is reported[7,120] to have a 'mild' negative impact on patients' HRQoL, possibly attributable to the high rates of AEs experienced by patients in DECISION.

Cost-effectiveness evidence

The two submitting companies and the AG agree that there are no published cost-effectiveness studies relevant to the decision problem set out in the final scope issued by NICE.[53] The AG considered that none of the cost-effectiveness studies identified via the AG's literature review were carried out from a NHS England perspective and that, when treatment with lenvatinib and sorafenib were compared, the results were based on the results of flawed indirect comparisons. In addition, the prices of the drugs reported in the studies were generally not consistent with the discounted prices that will likely be charged in the NHS in England. As a result of the absence of relevant published evidence, the AG developed a de novo cost-effectiveness model for the specific purpose of this appraisal and carried out several cost-effectiveness comparisons.

As the AG did not consider that it was appropriate to carry out an indirect comparison, the AG compared the cost-effectiveness of treatment with lenvatinib with the cost-effectiveness of BSC (using data from SELECT) and the cost-effectiveness of treatment with sorafenib with the cost-effectiveness of BSC (using data from DECISION). The AG also compared the cost-effectiveness of each of the SELECT and DECISION intervention drugs with BSC data from the other trial as a sensitivity analysis.

In the AG's base-case analysis, using list prices only, the comparison of treatment with lenvatinib versus BSC yields an ICER per QALY gained of £65,872, and the comparison of treatment with sorafenib versus BSC yields an ICER per QALY gained of £85,644. The base-case deterministic and probabilistic results were similar for both comparisons. The AG's deterministic sensitivity analysis involved varying 18 parameters; the results showed that none of the variations lowered the AG's base-case ICERs to < £50,000 per QALY gained.

When the AG compared the cost-effectiveness of treatment with lenvatinib with the cost-effectiveness of BSC (using placebo data from SELECT) and the cost-effectiveness of treatment with sorafenib with the cost-effectiveness of BSC (placebo data from DECISION), the ICERs per QALY gained were approximately doubled (£130,592) and halved (£41,716), respectively. These results confirm that the choice of BSC comparator is hugely influential in this appraisal.

Strengths and limitations of the assessment

Strengths

A key strength of this review is that it has brought together all of the available relevant evidence (RCTs, observational studies, systematic reviews, indirect comparisons and cost-effectiveness studies) for assessing the clinical and cost-effectiveness of treatment with lenvatinib versus sorafenib in patients with RR-DTC.

The wide array of clinical results available demonstrate that treatment with lenvatinib is more effective when compared with placebo/BSC for all patients and that prior VEGFR-targeted therapy (or even a treatment delay) does not influence the potential for a patient to benefit from treatment.

Another strength of the research is the AG's detailed investigation of the PFS (and OS) risk profiles of the patients in the two main trials. The AG's analytical critique shows that the assumptions of PH underpinning the indirect comparison calculations are violated and explains why data from these two trials should not be compared in an indirect comparison. The AG's critique challenges the validity of published indirect comparison results[7,8,57,97] as well as those from published economic evaluations[7,8,38,160,162] that have used indirect comparison results in their analyses.

The results from the AG's economic analyses demonstrate that the choice of BSC comparator has a big influence on the size of the estimated ICERs per QALY gained.

Limitations

The main limitation of this review is that the AG was unable to compare the clinical effectiveness and cost-effectiveness of lenvatinib with those of sorafenib. The AG did not consider that it was appropriate to conduct an indirect comparison because of key differences in the intervention and placebo arms of SELECT and DECISION (both within and across the trials) and because the results of AG analyses demonstrated that the risk profiles of the patients in the placebo arms were different. Therefore, the AG concluded that it was not possible to determine the comparative clinical effectiveness and cost-effectiveness of lenvatinib versus sorafenib; this is problematic as lenvatinib and sorafenib are two relatively new treatments that appear to work well compared with placebo/BSC for patients with RR-DTC who have limited treatment options.

Uncertainties

Although it is recommended[4,23–25] that only patients who are symptomatic and/or have rapidly progressing disease are treated with lenvatinib or sorafenib, it is unclear how many patients in SELECT and DECISION met these criteria. As there are no universally accepted objective criteria for describing patients who are symptomatic and/or rapidly progressing, it is difficult to retrospectively identify these groups of patients with any confidence.

Therefore, it is unclear whether or not the efficacy findings from SELECT and DECISION differ in patients who are symptomatic and/or rapidly progressing compared with those who are not. It is also unknown whether or not the frequency and type of AEs differ between these groups of patients and/or whether patient HRQoL is also influenced by symptom status.

There is considerable uncertainty around the HRQoL of patients with RR-DTC in general. Although it appears that treatment with sorafenib may have a 'mild' negative impact on HRQoL, the HRQoL data collected during DECISION were limited. As HRQoL data were not collected as part of SELECT, the impact of treatment with lenvatinib on HRQoL, whether positive or negative, is unknown. To what extent a patient's HRQoL is affected by their symptom status (symptomatic vs. asymptomatic) is also unknown.

Although, for patients with RR-DTC, RCT evidence has shown clinically meaningful improvements in PFS for those treated with lenvatinib and sorafenib compared with placebo, the question remains whether treatment with lenvatinib or sorafenib can deliver a true OS benefit to patients. The adjusted RPSFTM OS estimates suggest that this may be the case for patients treated with lenvatinib but not for patients treated with sorafenib.

Other relevant factors

The AG considers that it is important to reiterate that the cost–utility analyses presented in this MTA report are based on list prices only. As lenvatinib has a confidential PAS price and sorafenib has a confidential Commercial Unit Access price, the cost-effectiveness comparisons presented in this AG report cannot be used as the basis for decision-making. The AG provided cost-effectiveness results generated using the discounted prices for lenvatinib and sorafenib in a confidential appendix presented to NICE.

Chapter 7 Conclusions

Compared with placebo, treatment with lenvatinib or sorafenib results in an improvement in PFS, ORR and, possibly, OS. However, compared with placebo, both drugs also increase the incidence of AEs, in particular hypertension, hand–foot syndrome and diarrhoea. Dose reductions with both drugs are, therefore, frequently required.

The AG considers that it is not possible to compare the clinical effectiveness or cost-effectiveness of lenvatinib with those of sorafenib. Primarily, this is because the risk profiles of the patients in the placebo arms of SELECT and DECISION do not appear to be comparable.

Using list prices, compared with BSC, both treatments exhibit estimated ICERs of > £50,000 per QALY gained. Compared with BSC, the probability of sorafenib being cost-effective at a threshold of £50,000 per QALY gained is < 0.05% and the probability of lenvatinib being cost-effective is 5.4%.

Suggested research priorities

In order of priority, the AG suggests the following further research priorities:

1. Head-to-head RCT evidence.

    i. Clinical advice to the AG is that only RR-DTC patients experiencing symptoms, or those who have clinically significant progressive disease, are likely to be treated in routine clinical practice. Subgroup analyses suggest that the effects on PFS are similar for patients treated with sorafenib regardless of whether they are symptomatic or asymptomatic. However, these findings are post hoc and include only a minority of symptomatic patients. It is unclear if other outcomes, such as OS, ORR, AEs and HRQoL, differ by symptomatic or asymptomatic disease. Future studies of patients should aim to include a greater proportion of patients with symptomatic disease and investigate possible differences. Consideration should be given to using the classification of patients as symptomatic or asymptomatic as a randomisation stratification factor.
    ii. It would be useful to record, and report, HRQoL outcomes from any future clinical study of lenvatinib and sorafenib. In particular, data should be collected, using the EQ-5D questionnaire, throughout the whole trial period, not only from patients whose disease has not progressed. Further research on HRQoL from treating patients who have symptomatic disease compared with those who do not is also required.
    iii. Currently, evidence does not allow a comparison of the effectiveness of treatment with lenvatinib with the effectiveness of treatment with sorafenib. A head-to-head trial considering these treatments and placebo would generate results that would be valuable to decision-makers.
    iv. It would be useful to explore how lenvatinib, sorafenib and BSC should be positioned in the treatment pathway.

2. Statistical research.

    i. The AG considers that it is important to explore more than just standard differences in participant and trial characteristics when considering the heterogeneity of studies that may be included in an indirect comparison. The AG suggests that, before undertaking an indirect comparison, the risk profiles of patient populations for the relevant outcome should be checked to confirm that they are proportional both within and across all trials that are being considered for inclusion in the network. This assessment would avoid generating indirect comparison results that are of unknown reliability.

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Contributions of authors

Nigel Fleeman (Research Fellow, University of Liverpool) reviewed the evidence for clinical effectiveness, including study selection, data extraction, synthesis and interpretation. He contributed to the study selection for inclusion into the cost-effectiveness review and provided editorial input.

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Adrian Bagust (Professor of Health Modelling, University of Liverpool) developed the de novo economic model.

Marty Richardson [Research Associate (Medical Statistician), University of Liverpool] provided statistical advice and quality assessment of the systematic reviews included in the clinical effectiveness review.

Sophie Beale [Research Associate (Decision Analyst), University of Liverpool] interpreted the clinical effectiveness and cost-effectiveness evidence, summarised the company economic models and provided editorial input.

Angela Boland (Associate Director, University of Liverpool) interpreted the clinical effectiveness and cost-effectiveness evidence and provided editorial input.

Yenal Dundar (Research Fellow, University of Liverpool) contributed to data extraction and the quality assessment of studies included in the clinical effectiveness review.

Janette Greenhalgh [Senior Research Fellow (Clinical Effectiveness), University of Liverpool] contributed to data extraction and the quality assessment of studies included in the clinical effectiveness review.

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All authors contributed to the writing of the report.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Appendix 1 Literature search strategies

Search strategies for evidence of clinical effectiveness

EMBASE

Date searched: 10 January 2017.

Search from 1980 to 2017 week 2.

1	exp Thyroid Neoplasms/
2	((thyroid* or papillar* or follicular*) adj4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*)).tw.
3	(DTC or FTC or PTC).tw.
4	adenocarcinoma, follicular/ or carcinoma, papillary, follicular/ or adenocarcinoma, papillary/
5	1 or 2 or 3 or 4
6	(Lenvatinib or Lenvima or E7080).tw.
7	(Nexavar or Sorafenib or bay439006).tw.
8	lenvatinib/
9	sorafenib/
10	6 or 7 or 8 or 9
11	5 and 10
12	limit 11 to yr='1999 -Current'

MEDLINE

Date searched: 10 January 2017.

1	exp Thyroid Neoplasms/
2	((thyroid* or papillar* or follicular*) adj4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*)).tw.
3	(DTC or FTC or PTC).tw.
4	adenocarcinoma, follicular/ or carcinoma, papillary, follicular/ or adenocarcinoma, papillary/
5	1 or 2 or 3 or 4
6	(Lenvatinib or Lenvima or E7080).tw.
7	(Nexavar or Sorafenib or bay439006).tw.
8	6 or 7
9	5 and 8
10	limit 9 to yr='1999 -Current'

PubMed

Date searched: 10 January 2017.

#1	Search (((thyroid* or papillar* or follicular*))) AND ((Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))
#2	Search (DTC or FTC or PTC)
#3	Search (#1 or #2)
#4	Search (Lenvatinib or Lenvima or E7080 or Nexavar or Sorafenib or bay439006)
#5	Search (#3 and #4)
#6	Search ('2016/07/01'[Date - Entrez] : '3000'[Date - Entrez])
#7	Search (#5 and #6)

The Cochrane Library (Cochrane Database of Systematic Review/Cochrane Central Register of Controlled Trials/Database of Abstracts of Reviews of Effects/Health Technology Assessment Database)

Date searched: 10 January 2017.

#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or papillar* or follicular*) near/4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))
#3	(DTC or FTC or PTC)
#4	MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees
#5	MeSH descriptor: [Carcinoma, Papillary, Follicular] explode all trees
#6	MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	(Lenvatinib or Lenvima or E7080)
#9	(Nexavar or Sorafenib or bay439006)
#10	#8 or #9
#11	#7 and #10 Publication Year from 1999 to 2017

Economic filter for database search

EMBASE

Date searched: 10 January 2017.

1	exp Thyroid Neoplasms/
2	((thyroid* or papillar* or follicular*) adj4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*)).tw.
3	(DTC or FTC or PTC).tw.
4	adenocarcinoma, follicular/ or carcinoma, papillary, follicular/ or adenocarcinoma, papillary/
5	1 or 2 or 3 or 4
6	(Lenvatinib or Lenvima or E7080).tw.
7	(Nexavar or Sorafenib or bay439006).tw.
8	lenvatinib/

9	sorafenib/
10	6 or 7 or 8 or 9
11	5 and 10
12	limit 11 to yr='1999 -Current'
13	Socioeconomics/
14	Cost benefit analysis/
15	Cost effectiveness analysis/
16	Cost of illness/
17	Cost control/
18	Economic aspect/
19	Financial management/
20	Health care cost/
21	Health care financing/
22	Health economics/
23	Hospital cost/
24	(fiscal or financial or finance or funding).tw.
25	Cost minimization analysis/
26	(cost adj estimate$).mp.
27	(cost adj variable$).mp.
28	(unit adj cost$).mp.
29	or/13-28
30	12 and 29

MEDLINE

Date searched: 10 January 2017.

1	exp Thyroid Neoplasms/
2	((thyroid* or papillar* or follicular*) adj4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*)).tw.
3	(DTC or FTC or PTC).tw.
4	adenocarcinoma, follicular/ or carcinoma, papillary, follicular/ or adenocarcinoma, papillary/
5	1 or 2 or 3 or 4
6	(Lenvatinib or Lenvima or E7080).tw.
7	(Nexavar or Sorafenib or bay439006).tw.
8	6 or 7
9	5 and 8
10	Economics/
11	'costs and cost analysis'/
12	Cost allocation/
13	Cost-benefit analysis/
14	Cost control/

15	Cost savings/
16	Cost of illness/
17	Cost sharing/
18	'deductibles and coinsurance'/
19	Medical savings accounts/
20	Health care costs/
21	Direct service costs/
22	Drug costs/
23	Employer health costs/
24	Hospital costs/
25	Health expenditures/
26	Capital expenditures/
27	Value of life/
28	exp economics, hospital/
29	exp economics, medical/
30	Economics, nursing/
31	Economics, pharmaceutical/
32	exp 'fees and charges'/
33	exp budgets/
34	(low adj cost).mp.
35	(high adj cost).mp.
36	(health?care adj cost$).mp.
37	(fiscal or funding or financial or finance).tw.
38	(cost adj estimate$).mp.
39	(cost adj variable).mp.
40	(unit adj cost$).mp.
41	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
42	or/10-41
43	9 and 42

The Cochrane Library (NHS Economic Evaluation Database)

Date searched: 10 January 2017.

#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	(thyroid* near/4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))
#3	DTC or FTC or PTC
#4	#1 or #2 or #3
#5	(Lenvatinib or Lenvima or E7080 or Nexavar or Sorafenib or bay439006)
#6	#4 and #5

EconLit

Date searched: 10 January 2017.

(thyroid* N4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))

Appendix 2 Table of excluded studies with rationale

The studies excluded by the AG at screening stage 2 are summarised in *Table 32*.

TABLE 32 References excluded at screening stage 2 (full-text stage)

Study and year of publication	Reason for exclusion
Abbadessa *et al.* 2006[180]	Wrong study design
Alonso-Gordoa *et al.* 2015[181]	Wrong study design
Andrews 2013[182]	Wrong study design
Anonymous 2013[183]	Wrong study design
Anonymous 2013[184]	Wrong study design
Anonymous 2014[185]	Wrong study design
Anonymous 2015[186]	Wrong study design
Anonymous 2015[187]	Wrong study design
Anonymous 2016[188]	Wrong study design
Anonymous 2016[189]	Wrong study design
Antonelli 2014[190]	Wrong study design
Baudin *et al.* 2005[191]	Wrong study design
Belum *et al.* 2015[192]	Wrong population
Benvenga 2011[194]	Wrong study design
Bernet and Smallridge 2014[195]	Wrong study design
Bible 2012[196]	Wrong study design
Bikas *et al.* 2016[197]	Wrong study design
Blair and Plosker 2015[198]	Wrong study design
Boudou-Rouquette 2015[199]	Wrong study design
Bradford Carter *et al.* 2011[200]	Wrong study design
Brose 2009[201]	Wrong study design
Brose *et al.* 2015[156]	Wrong study design
Butler 2015[202]	Wrong study design
Cabanillas and Habra 2016[203]	Wrong study design
Cabanillas *et al.* 2011[204]	Wrong study design
Capdevila *et al.* 2010[205]	Wrong study design
Cappagli *et al.* 2011[206]	Wrong study design
Clayman 2015[207]	Wrong study design
Cooper *et al.* 2009[208]	Wrong study design
Corrado *et al.* 2017[209]	Wrong study design

continued

TABLE 32 References excluded at screening stage 2 (full-text stage) (*continued*)

Study and year of publication	Reason for exclusion
Costa *et al.* 2016[210]	Wrong study design
Covell and Ganti 2015[42]	Wrong study design
Cully 2015[211]	Wrong study design
De La Fouchardiere *et al.* 2013[212]	Wrong study design
De Lartigue 2015[213]	Wrong study design
Deshpande *et al.* 2008[214]	Wrong study design
Dezso 2015[215]	Wrong study design
Droz *et al.* 2010[216]	Wrong study design
Duntas and Bernardini 2010[217]	Wrong study design
Fala 2015[218]	Wrong study design
Fallahi *et al.* 2013[219]	Wrong study design
Féliz and Tsimberidou 2013[220]	Wrong population
Funakoshi 2013[221]	Wrong population
Gadaleta-Caldarola *et al.* 2015[222]	Wrong study design
Ghatalia *et al.* 2015[223]	Wrong population
Ghatalia *et al.* 2015 [224]	Wrong population
Giuffrida *et al.* 2012[225]	Wrong population
Gyawali *et al.* 2016[226]	Wrong population
Haddad 2014[227]	Wrong study design
Hannallah *et al.* 2013[228]	Wrong study design
Haraldsdottir and Shah 2014[229]	Wrong study design
Hasskarl 2014[230]	Wrong study design
Haugen *et al.* 2016[24]	Wrong study design
Hesselink 2014[231]	Wrong population
Hewett *et al.* 2018[232]	Wrong study design
Ho and Sherman 2011[193]	Wrong study design
Hodak and Carty 2009[233]	Wrong study design
Hoftijzer *et al.* 2011[234]	Wrong study design
Hong *et al.* 2010[235]	Wrong population
Hong *et al.* 2014[236]	Wrong population
Ibrahim *et al.* 2012[237]	Wrong study design
Ito *et al.* 2016[238]	Wrong study design
Iwasaki *et al.* 2015[239]	Wrong study design
Iwasaki *et al.* 2016[240]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Iyer *et al.* 2010[241]	Wrong study design
Kapiteijn *et al.* 2012[242]	Wrong population (too broad)
Killock 2015[243]	Wrong study design
Klein Hesselink *et al.* 2015[244]	Wrong population (too broad)

TABLE 32 References excluded at screening stage 2 (full-text stage) (*continued*)

Study and year of publication	Reason for exclusion
Kojic *et al.* 2012[245]	Wrong study design
Krajewska and Jarzab 2014[246]	Wrong study design
Krajewska *et al.* 2015[247]	Wrong study design
Krajewska *et al.* 2016[248]	Wrong study design
Krajewska *et al.* 2015[249]	Wrong study design
Launay-Vacher *et al.* 2015[250]	Wrong study design
Lerch and Richter 2012[251]	Wrong population (too broad)
Liu *et al.* 2016[252]	Wrong population (too broad)
Liu *et al.* 2014[253]	Wrong study design
Lorusso and Newbold 2015[254]	Wrong study design
Lorusso *et al.* 2016[255]	Wrong study design
Ma *et al.* 2015[256]	Wrong population
Majethia *et al.* 2016[257]	Wrong study design
Marotta *et al.* 2013[148]	Wrong study design
Mayor 2015[258]	Wrong study design
Moreo *et al.* 2016[259]	Wrong population
Nair *et al.* 2015[260]	Wrong study design
Nixon *et al.* 2013[261]	Wrong study design
Okamoto *et al.* 2015[262]	Wrong study design
Pacini *et al.* 2009[263]	Wrong study design
Pall 2013[264]	Wrong study design
Pall 2014[265]	Wrong study design
Pfister and Fagin 2008[266]	Wrong study design
Puxeddu *et al.* 2011[267]	Wrong study design
Qi *et al.* 2013[268]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Qi *et al.* 2013[269]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Qi *et al.* 2014[270]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Ramadan *et al.* 2012[271]	Wrong study design
Sacks and Braunstein 2014[34]	Wrong study design
Safavi 2012[272]	Wrong population
Saiyed *et al.* 2015[273]	Wrong population
Schlumberger 2010[274]	Wrong study design
Schlumberger 2011[275]	Wrong study design
Schutt and Eberhardt 2010[276]	Wrong population
Sherman 2008[277]	Wrong study design
Sherman 2009[278]	Wrong study design
Sherman *et al.* 2012[279]	Wrong intervention (not sorafenib monotherapy)

continued

TABLE 32 References excluded at screening stage 2 (full-text stage) (*continued*)

Study and year of publication	Reason for exclusion
Sherman *et al.* 2013[280]	Wrong intervention (not sorafenib monotherapy)
Sherman *et al.* 2015[281]	Wrong intervention (not sorafenib monotherapy)
Shojaei 2012[282]	Wrong study design
Smit *et al.* 2016[283]	Wrong study design
Takahashi 2014[284]	Wrong study design
Terada *et al.* 2015[285]	Wrong study design
Thanigaimani *et al.* 2011[286]	Wrong study design
Tracy and Roman 2016[287]	Wrong study design
Tremblay *et al.* 2015[288]	Wrong study design (reports the findings from a matched ITC but no reporting of a systematic review)
Tremblay *et al.* 2015[289]	Wrong study design [reports the findings (number needed to treat) from an ITC but no reporting of a systematic review]
Tremblay *et al.* 2015[290]	Wrong study design (reports the findings from a matched ITC but no reporting of a systematic review)
Tremblay *et al.* 2016[291]	Wrong study design (cost-effectiveness methods paper)
Tsimberidou *et al.* 2009[292]	Wrong interventions
Tu *et al.* 2016[293]	Wrong study design
Tuttle and Leboeuf 2007[294]	Wrong study design
Tuttle *et al.* 2014[295]	Wrong study design
Vetter 2014[296]	Wrong study design
Wagner *et al.* 2015[297]	Wrong study design
Warpakowski 2014[298]	In German
Wendling 2013[299]	Wrong study design
Wirth 2015[300]	Wrong study design
Wong and Lang 2012[301]	Wrong study design
Worcester 2015[302]	Wrong study design
Yang *et al.* 2015[303]	Wrong population
Yang *et al.* 2017[304]	Wrong population
Yeung and Cohen 2015[305]	Wrong study design
Yimaer *et al.* 2016[306]	Wrong population
Zhu *et al.* 2016[307]	Wrong population
Zygulska *et al.* 2013[308]	Wrong study design

Appendix 3 Data extraction tables from randomised controlled trials not presented in the main body of the report

TABLE 33 Patients included and excluded in SELECT and DECISION

	Study	
Criteria	SELECT	DECISION
Inclusion	• Adults with histologically or cytologically confirmed diagnosis of DTC • Measurable disease as confirmed by central radiographic review within the past 13 months • Radioactive iodine-refractory/resistant (see *Table 34* for definition) • Disease progressed within 12 (+ 1) months according to RECIST 1.1, assessed and confirmed by central radiographic review of CT and/or MRI scans • ECOG PS 0 to 2 • None or one prior VEGFR-targeted therapy • Adequately controlled blood pressure with or without antihypertensive medications • Adequate bone marrow, blood coagulation, liver and renal function	• Adults with differentiated and poorly DTC • One or more measurable lesion by CT or MRI according to RECIST 1.0 • Disease progressed within the past 14 months according to RECIST 1.0 • Radioactive iodine resistant (see *Table 34* for definition) • ECOG PS of 0–2 • Patients must not be candidates for curative surgery or radiation therapy • Adequate TSH suppression (< 0.5 mIU/L) • Adequate bone marrow, liver and renal function
Exclusion	• Anaplastic or medullary carcinoma of the thyroid • Active malignancy (except for differentiated thyroid carcinoma, or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix) within the past 24 months • Prior treatment with lenvatinib • Two or more prior VEGFR-targeted therapies or any ongoing treatments for RR-DTC other than TSH-suppressive thyroid hormone therapy • Major surgery within 3 weeks prior to the first dose of study drug • Patients with urine protein of ≥ 1 g/24 hours • Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib in the opinion of the investigator • Significant cardiovascular impairment • Prolongation of QTc to > 480 ms • Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalised ratio (INR) monitoring (treatment with low-molecular-weight heparin is allowed) • Active haemoptysis within 3 weeks prior to the first dose of study drug • Active infection (any infection requiring treatment) • Any medical or other condition that, in the opinion of the investigator, would preclude participation in a clinical trial • Women who are pregnant or breastfeeding • Known intolerance to any of the study drugs (or any of the excipients)	• Concurrent cancer distinct in primary site or histology from thyroid cancer ≤ 5 years prior to randomisation (except for cervical cancer in situ, treated basal cell carcinoma, and superficial bladder tumours) and patients with foci of undifferentiated thyroid cancer • Patients who had received previous targeted therapy, thalidomide, or chemotherapy for thyroid cancer (low-dose chemotherapy for radio sensitisation was allowed) • Patients who undergo major surgery, open biopsy or significant traumatic injury ≤ 30 days prior to randomisation • Presence of a non-healing wound, ulcer, bone fracture, or grade ≥ 2 infection according to NCI-CTCAE v3.0[309] • Grade ≥ 3 haemorrhage or bleeding event according to NCI-CTCAE ≤ 3 months prior to randomisation • Evidence or history of bleeding diathesis or coagulopathy; or the presence of tracheal, bronchial or oesophageal infiltration with significant risk of bleeding (but without having received local treatment prior to enrolment in the study) • Patients with clinically significant cardiac disease and/or uncontrolled hypertension (> 150/90 mmHg) despite optimal treatment • Patients known to be infected with HIV or hepatitis B or C virus • Women who are pregnant or breastfeeding • Patients with a known or suspected allergy to sorafenib or hypersensitivity to sorafenib or any agent given during the course of the study

HIV, human immunodeficiency virus; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QTc, QT corrected interval.

Note

Information drawn from Schlumberger *et al.*,[51] including supplementary material (protocol), Brose *et al.*[52,72]

TABLE 34 Definitions of DTC refractory to radioactive iodine employed by SELECT and DECISION

Criteria	Study	
	SELECT	DECISION
To be classified as having DTC refractory to radioactive iodine, patients were required to meet at least one of the criteria specified	• At least one measurable lesion that does not demonstrate iodine uptake on any radioactive iodine scan • At least one measurable lesion that had progressed, according to RECIST 1.1, within 12 months of radioactive iodine therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning (these were patients who were not eligible for possible curative surgery) • Cumulative activity of radioactive iodine of > 600 mCi or 22 GBq, with the last dose administered ≥ 6 months prior to study entry	• At least one target lesion without iodine uptake • Tumours had iodine uptake and progressed after one radioactive iodine treatment [≥ 3.7 GBq (≥ 100 mCi)] within the past 16 months • Disease progression after each of two radioactive iodine treatments [≥ 3.7 GBq (≥ 100 mCi)] within 16 months of each other (with the last such treatment administered > 16 months ago) • Cumulative radioactive iodine activity of ≥ 22.2 GBq (≥ 600 mCi)

GBq, gigabecquerels; mCi, millicurie.
Note
Information drawn from Schlumberger *et al.*,[51] including supplementary material (protocol), Brose *et al.*[52,72]

TABLE 35 Concomitant treatment available to patients in SELECT and DECISION

Concomitant treatment allowed and disallowed	Study	
	SELECT	DECISION
Permitted	• Thyroxine suppression therapy • Over-the-counter medications • Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics and antidiarrheal drugs) may be given at investigator discretion, unless expected to interfere with the evaluation of (or to interact with) study drug • Aspirin, nonsteroidal anti-inflammatory drugs and low-molecular-weight heparin are permissible but should be used with caution • G-CSF or equivalent may be used in accordance with ASCO, institutional or national guidelines • Erythropoietin may be used according to ASCO, institutional or national guidelines, but the patient should be carefully monitored for increases in red blood cell counts	• Thyroid hormone replacement with suppressed TSH levels (target of < 0.5 mU/l) • Treatment with non-conventional therapies (e.g. herbs with the exception of Saint John's wort or acupuncture) and vitamin/mineral supplements provided that they do not interfere with the study end points, in the opinion of the investigator • Bisphosphonate treatment in patients with bone metastasis at discretion of the investigator • G-CSF and other haematopoietic growth factors may be used during the study of the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the discretion of the investigator; however, they may not be substituted for a required dose reduction (patients taking chronic erythropoietin are permitted) • Narrow therapeutic index medication (e.g. warfarin) permitted with monitoring
Prohibited	• Anti-cancer therapies, such as chemotherapy, palliative radiotherapy or immunotherapy	• Concomitant radioactive iodine, chemotherapy or other investigational therapy • Substances known to induce CYP3A4

ASCO, American Society of Clinical Oncology; G-CSF, granulocyte colony-stimulating factor.
Note
Information drawn from Schlumberger *et al.*[51] [supplementary material (protocol)], Brose *et al.*[72] and Bayer HealthCare.[310]

TABLE 36 Length of follow-up and average dose intensity in SELECT and DECISION

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib ($n = 261$)	Placebo ($n = 131$)	Sorafenib ($n = 207$)	Placebo ($n = 210$)
First data cut-off point	***November 2013***		***August 2012***	
Length of follow-up (months), median (95% CI)	17.1 (16.0 to 17.6)	17.4 (15.9 to 19.0)	17.4 (NR)	NR
Average dose (mg)	17.2	NR	651	793
Dose intensity (% of maximum dose)	71.7	NR	81.4	99.1
Second data cut-off point	***June 2014***		***May 2013***	
Length of follow-up (months), median (95% CI)	23.6 (22.7 to 24.5)	24.1 (22.1 to 26.1)	24.1 (NR)	NR
Average dose (mg)	NR	NR	NR	NR
Dose intensity (% of maximum dose)	NR	NR	NR	NR
Third data cut-off point	***August 2015***		***July 2015***	
Length of follow-up (months), median (95% CI)	37.8 (NR)	37.9 (NR)	36.0 (NR)	NR
Average dose (mg)	16.5[a]	NR	651.2	793.6
Dose intensity (% of maximum dose)	68.8[a]	NR	81.4	99.2

NR, not reported.
a Eisai Ltd's response to the AG's report to the NICE Appraisal Committee (7 September 2017).[311]
Note
Information drawn from Schlumberger *et al.*,[51] Eisai Ltd,[8] Brose *et al.*,[52] Bayer HealthCare[7] and Eisai Ltd's response to the AG's report to the NICE Appraisal Committee (7 September 2017).

TABLE 37 Subgroup analyses conducted in SELECT and DECISION

Study	
SELECT	DECISION
Prespecified subgroup analyses	
Age (≤ 65 years or > 65 years)	Age (< 60 years or ≥ 60 years)
Geographic region (Europe, North America or other)	Geographical region (North America, Europe or Asia)
Prior VEGF-targeted therapy (0 or 1)	Sex (male or female)
Sex (male or female)	Histology (PTC, FTC: Hürthle cell, FTC: other subtypes, or poorly differentiated)
Race (white or non-white)	Site of metastasis [bone (yes or no) and lung only (yes or no)]
Histology (PTC or FTC)	2-[^{18}F]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) uptake (negative or positive)
TSH (≤ 0.5, > 0.5 to 2.0, > 2.0 to 5.5 or > 5.5 ml/UL)	Prior radioactive iodine cumulative dosing [< 600 mCi (22.2 GBq) or ≥ 600 mCi (22.2 GBq)]
	Tumour burden as measured by number of target or non-target lesions (fewer than median or at least median)
	Tumour burden as measured by sum of target diameters (less than median or at least median)

continued

TABLE 37 Subgroup analyses conducted in SELECT and DECISION (*continued*)

Study	
SELECT	**DECISION**
Post hoc subgroup analyses	
Number of sites of metastasis (1, 2, 3 or ≥ 4)[a]	BRAF status (wild type or mutant)[a]
Site of metastasis (brain, bone, liver, lung or lymph node)[a]	RAS status (wild type or mutant)[a]
Site of metastasis [bone (yes or no) and lung (yes or no)]	TSH levels [less than median (449.4 ng/mL) or at least median (449.4 ng/m)][a]
Target tumour size (≤ 35 mm, 36–60 mm, 91–92 mm or ≥ 92 mm)	Maximum tumour size (< 1.5 cm or ≥ 1.5 cm)
BRAF status (wild type or mutant)	Category of lesion size (< 1.5 cm, ≥ 1.5 cm, < 2 cm, ≥ 2 cm, < 3 cm, ≥ 3 cm, < 4 cm or ≥ 4 cm)
RAS status (wild type or mutant)	Lesion category: number of target lesions (< 3, ≥ 3, < 4, ≥ 4, < 5 or ≥ 5)[b]
TSH levels (≤ 0.5, 0.5 to 2.0 or > 2.0 ml/UL)	Symptomatic or asymptomatic at baseline[b,c]
Pharmacodynamic biomarkers [TG and CAF levels (Ang2, VEGF, sTie2, and FGF23)][a]	Subgroup analyses on safety parameters by region, body mass index, sex and age (full details not reported)[d]
Body mass index [underweight and normal weight (< 25 kg/m^2), overweight (25 kg/m^2 to 29.99 kg/m^2) and obese (≥ 30 kg/m^2)][a]	Subgroup analyses of baseline factors predictive of HRQoL (full details not reported)[d]
With or without treatment-emergent hypertension[a]	

BRAF, B-type rapidly accelerated fibrosarcoma; CAF, cytokine and angiogenic factor.
a Reported in conference abstracts.[71,84,90,112,132–134,312]
b Reported in Bayer HealthCare[7] (appendix 7.3).
c Reported in the EPAR for sorefanib.[26]
d Reported in Bayer HealthCare.[7]
Note
All of the analyses were reported in the primary published papers unless otherwise stated.

TABLE 38 Overall survival findings from SELECT and DECISION, including information on treatment crossover and subsequent treatment received

	Study			
	SELECT		**DECISION**	
Characteristic	**Lenvatinib (*N* = 261)**	**Placebo (*N* = 131)**	**Sorafenib (*N* = 207)**	**Placebo (*N* = 210)**
Received anti-cancer treatment following progression, *n* (%)	41 (15.7)	16 (12.2)	42 (20.3)	18 (8.6)
OS: first data cut-off point	***November 2013***		***August 2012***	
Patients who crossed over, *n* (%)	N/A	109 (83.2)	55 (26.6)	150 (71.4)
Deaths, *n* (%)	71 (27.2)	47 (35.9)	45 (21.7)	54 (25.7)
Median OS (months) (95% CI)	NE (22.0 to NE)	NE (14.3 to NE)	NE	NE
Unadjusted HR (95% CI); *p*-value	0.73 (0.50 to 1.07); 0.1032		0.80 (0.54 to 1.19); 0.14	

TABLE 38 Overall survival findings from SELECT and DECISION, including information on treatment crossover and subsequent treatment received (*continued*)

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
RPSFTM-adjusted HR (95% CI); *p*-value, cox method	NR		0.61 (0.40 to 0.94); 0.0125	
RPSFTM-adjusted HR (95% CI); *p*-value, bootstrapping method	0.62 (0.40 to 1.00); 0.0510		0.61 (0.18 to 2.16); NR	
IPE-adjusted HR (95% CI); *p*-value, cox method	N/A		0.70 (0.47 to 1.04); 0.0388	
IPE-adjusted HR (95% CI); *p*-value, bootstrapping method	N/A		0.70 (0.40 to 1.38); NR	
OS: second data cut-off point	***June 2014***		***May 2013***	
Patients who crossed over, *n* (%)	N/A	115 (87.8)	NR	157 (74.8)
Deaths, *n* (%)	93 (35.6)	55 (42.0)	66 (31.9)	72 (34.3)
Median OS (months) (95% CI)	NE (30.9 to NE)	19.1 (21.7 to NE)	NE	36.5 (32.2 to NE)
Unadjusted HR (95% CI); *p*-value	0.80 (0.57 to 1.12) nominal $p = 0.1993$		0.88 (0.63 to 1.24); 0.24	
RPSFTM-adjusted HR (95% CI); *p*-value, cox method	NR		0.69 (0.49 to 0.99); NR	
RPSFTM-adjusted HR (95% CI); *p*-value, bootstrapping method	0.53; nominal $p = 0.0051$ (0.34 to 0.82)		0.69 (0.33 to 1.65); NR	
IPE-adjusted HR (95% CI); *p*-value, cox method	N/A		0.79 (0.57 to 1.11); NR	
IPE-adjusted HR (95% CI); p-value, bootstrapping method	N/A		0.79 (0.46 to 1.61); NR	
OS: third data cut-off point	***August 2015***		***July 2015***	
Patients who crossed over, *n* (%)	N/A	115 (87.8)	NR	158 (75.0)
Deaths, *n* (%)	121 (46.4)	70 (53.4)	103 (49.8)	109 (51.9)
Median OS (months) (95% CI)	41.6 (31.2 to NE)	34.5 (21.7 to NE)	39.4 (32.7 to 51.4)	42.8 (34.7 to 52.6)
Unadjusted HR (95% CI); *p*-value	0.84 (0.62 to 1.13) nominal $p = 0.2475$		0.92 (0.71 to 1.21) one-sided $p = 0.28$	
RPSFTM-adjusted HR (95% CI); *p*-value, cox method	NR		0.77 (0.58 to 1.02); NR	
RPSFTM-adjusted HR (95% CI); *p*-value, bootstrapping method	0.54; nominal $p = 0.0025$ (0.36 to 0.80)		0.77 (0.42 to 1.79); NR	
IPE-adjusted HR (95% CI); *p*-value, cox method	N/A		0.80 (0.61 to 1.05); NR	
IPE-adjusted HR (95% CI); *p*-value, bootstrapping method	N/A		0.80 (0.48 to 1.71); NR	

N/A, not applicable; NE, not estimable; NR, not reported.

Note

Information drawn from Eisai Ltd[8] (table 8), Eisai Ltd's *Data on File*. 2016; not publically available. *SELECT August 2015 Data Cut* (table 14.2.2.1.1a and table 14.2.2.1.2a) and Bayer HealthCare[7] (table 7 and text on pages 29 and 30).

TABLE 39 Subsequent treatment received in SELECT and DECISION following disease progression (first data cut-off points)

Characteristic	Study			
	SELECT, *n* (%)		DECISION, *n* (%)	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
Any anti-cancer treatment	41 (15.7)	16 (12.2)	42 (20.3)	18 (8.6)
Antineoplastic and immunomodulating agents	29 (11.1)	13 (9.9)	38 (18.4)	17 (8.1)
Various[a]	17 (6.5)	5 (3.8)	4 (1.9)	2 (1.0)

a Various includes the following categories: other therapeutic radiopharmaceuticals, all other therapeutic products, diagnostic agents and diagnostic radiopharmaceuticals.

Note

Information drawn from SELECT clinical study report (table 14.3.8.1) and DECISION clinical study report (table 14.1.2/11).

TABLE 40 Progression-free survival findings (by blinded review) from SELECT and DECISION

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
PFS by blinded review: first data cut-off point	November 2013		August 2012	
Events, *n* (%)	93 (35.6)	109 (83.2)	113 (54.6)	137 (65.2)
Died before progression, *n* (%)	14 (5.4)	4 (3.1)	NR	NR
Median PFS (months) (95% CI)	18.3 (15.1 to NE)	3.6 (2.2 to 3.7)	10.8	5.8
Stratified HR (95% CI); *p*-value	0.21 (0.14 to 0.31); < 0.001		0.59 (0.45 to 0.76); < 0.0001	

NE, not estimable; NR, not reported.

Notes

Only investigator-assessed PFS has been reported for subsequent data cut-off points (see *Table 41*).

Information drawn from Schlumberger *et al.*[51] and Brose *et al.*[52]

TABLE 41 Progression-free survival findings (by investigator assessment) from SELECT and DECISION

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
PFS by investigator: first data cut-off point	***November 2013***		***August 2012***	
Events, *n* (%)	91 (34.9)	104 (79.4)	140 (67.6)	184 (87.6)
Died before progression, *n* (%)	16 (6.1)	6 (4.6)	NR	NR
Median PFS (months) (95% CI)	16.6 (4.8 to NE)	3.7 (3.5 to NE)	10.8	5.4
Stratified HR (95% CI); *p*-value	0.24 (0.16 to 0.35); < 0.001		0.49 (0.39 to 0.61); < 0.0001	

TABLE 41 Progression-free survival findings (by investigator assessment) from SELECT and DECISION (*continued*)

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 210)
PFS by investigator: second data cut-off point	***June 2014***		***May 2013***	
Events, *n* (%)	N/A	N/A	N/A	N/A
Died before progression, *n* (%)	N/A	N/A	N/A	N/A
Median PFS (months) (95% CI)	N/A	N/A	N/A	N/A
Stratified HR (95% CI); *p*-value	N/A		N/A	
PFS by investigator: third data cut-off point	***August 2015***		***July 2015***	
Events, *n* (%)	121 (46.4)	107 (81.7)	N/A	N/A
Died before progression, *n* (%)	19 (7.3)	6 (4.6)	N/A	N/A
Median PFS (months) (95% CI)	19.4 (14.8 to 29.3)	3.7 (3.5 to 5.4)	N/A	N/A
Stratified HR (95% CI); *p*-value	0.24 (0.17 to 0.35); < 0.001		N/A	

N/A, not applicable; NE, not estimable; NR, not reported.
Note
Information drawn from Schlumberger *et al.*,[51] Eisai Ltd's *Data on File*. 2016; not publically available. *SELECT August 2015 Data Cut* (table 14.2.2.1.5a) and Brose *et al.*[52]

TABLE 42 Objective tumour response findings from SELECT and DECISION: first data cut-off point

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 196)	Placebo (*N* = 201)
ORR (%) (95% CI)	64.8 (59.0 to 70.5)	1.5 (0.0 to 3.6)	12.2 (8.0 to 17.7)	0.5 (0.0 to 2.7)
Difference (%) (95% CI)	63.2 (57.1 to 69.4)		11.7 (7.0 to 16.5)	
Odds ratio (95% CI); *p*-value	28.87 (12.46 to 66.86); < 0.0001		NR; < 0.0001	
Complete response, *n* (%)	4 (1.5)	0	0	0
Partial response, *n* (%)	165 (63.2)	2 (1.5)	24 (12.2)	1 (0.5)
Stable disease for ≥ 4 weeks	≥ 7 weeks: 60 (23.0)	≥ 7 weeks: 71 (54.2)	145 (74.0)	149 (74.1)
Durable stable disease (stable disease for ≥ 23 weeks or 6 months)	40 (15.3)	39 (29.8)	82 (41.8)	67 (33.2)
Progressive disease, *n* (%)	18 (6.9)	52 (39.7)	20 (10.2)	46 (22.9)
Patients unevaluable for response/not known, *n* (%)	1 (0.4)/13 (5.0)	2 (1.5)/4 (3.1)	N/A per-protocol analysis[a]	N/A per-protocol analysis[a]
Time to response (months)				
Median (95% CI)	2.0 (1.9 to 3.5)	5.6 (1.8 to 9.4)	NR	NR
Restricted mean (SD)	3.38 (0.18)	5.63 (3.79)	NR	NR

continued

TABLE 42 Objective tumour response findings from SELECT and DECISION: first data cut-off point (*continued*)

Characteristic	Study			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 196)	Placebo (*N* = 201)
Duration of response (months)				
Median (95% CI)	NE (16.8 to NE)	NE	10.2 (7.4 to 16.6)	NR
Restricted mean (SD)	17.34 (0.76)	NE	NR	NR

N/A, not applicable; NR, not reported.
a Unlike SELECT, patients who were unevaluable for response were excluded from the analyses in DECISION. There were 18 patients (4.3%) who were excluded from the objective tumour response analyses in DECISION: nine patients (4.3%) in each arm.
Note
Information drawn from Eisai Ltd,[8] EPAR for lenvatinib,[27] Bayer HealthCare and EPAR for sorafenib.[26]

TABLE 43 All-grade AEs reported by ≥ 30% of patients in any arm of SELECT and DECISION

Outcome	Study, *n* (%)			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 209)
Any AE	260 (99.6)	118 (90.1)	204 (98.6)	183 (87.6)
Hypertension	181 (69.3)	19 (14.5)	84 (40.6)	26 (12.4)
Diarrhoea	173 (66.3)	22 (16.8)	142 (68.6)	32 (15.3)
Decreased appetite/anorexia	139 (53.3)	24 (18.3)	66 (31.9)	10 (4.8)
Weight loss	132 (50.6)	19 (14.5)	97 (46.9)	29 (13.9)
Nausea	121 (46.4)	33 (25.2)	43 (20.8)	24 (11.5)
Fatigue	110 (42.1)	32 (24.4)	103 (49.8)	53 (25.4)
Headache	100 (38.3)	15 (11.5)	37 (17.9)	15 (7.2)
Stomatitis (oral mucositis)	93 (35.6)	9 (6.9)	48 (23.2)	7 (3.3)
Vomiting	92 (35.2)	19 (14.5)	23 (11.1)	12 (5.7)
Proteinuria	84 (32.2)	4 (3.1)	2 (1.0)	0 (0.0)
Hand–foot syndrome	84 (32.2)	1 (0.8)	158 (76.3)	20 (9.6)
Dysphonia	82 (31.4)	7 (5.3)	25 (12.1)	6 (2.9)
Rash or desquamation	48 (18.4)	2 (1.5)	104 (50.2)	24 (11.5)
Alopecia	32 (12.3)	7 (5.3)	139 (67.1)	16 (7.7)

Note
Information drawn from Eisai Ltd[8] and Brose *et al.*[52] [with additional data on proteinuria from the clinical study report for DECISION (table 14.3.3/4)].

TABLE 44 Grade ≥ 3 AEs reported by ≥ 1.5% of patients in any arm of SELECT and DECISION

	Study, *n* (%)			
	SELECT		DECISION	
Outcome	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 209)
Any grade ≥ 3 AE	223 (85.4)	39 (29.8)	133 (64.3)	63 (30.1)
Hypertension	112 (42.9)	5 (3.8)	20 (9.7)	5 (2.4)
Weight loss	31 (11.9)	1 (0.8)	12 (5.8)	2 (1.0)
Proteinuria	26 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	22 (8.4)	0 (0.0)	12 (5.8)	2 (1.0)
Decreased appetite/anorexia	15 (5.7)	1 (0.8)	5 (2.4)	0 (0.0)
Asthenia	15 (5.7)	3 (2.3)	0 (0.0)	0 (0.0)
Fatigue	12 (4.6)	2 (1.5)	12 (5.8)	3 (1.4)
Stomatitis (oral mucositis)	11 (4.2)	0 (0.0)	2 (1.0)	0 (0.0)
Hand–foot syndrome	9 (3.4)	0 (0.0)	42 (20.3)	0 (0.0)
Headache	8 (3.1)	1 (0.8)	0 (0.0)	0 (0.0)
Nausea	6 (2.3)	1 (0.8)	0 (0.0)	0 (0.0)
Hypocalcaemia	14 (5.4)	0 (0.0)	19 (9.2)	3 (1.4)
Dyspnoea	4 (1.5)	4 (3.1)	10 (4.8)	6 (2.9)
Dysphagia	4 (1.5)	4 (3.1)	3 (1.4)	2 (1.0)
Rash/desquamation	1 (0.4)	0 (0.0)	10 (4.8)	0 (0.0)

Note
Information drawn from Eisai Ltd,[8] Brose *et al.*[52] and Worden *et al.*[139] [with additional data from the clinical study report for SELECT (table 33) and from the clinical study report for DECISION (tables 14.3.3/4 and 14.3.3/1)].

TABLE 45 Serious AEs reported by ≥ 2% of patients in any arm of SELECT and DECISION

	Study, *n* (%)			
	SELECT[a]		DECISION	
Outcome	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 209)
SAEs	133 (51.0)	31 (23.7)	77 (37.2)	55 (26.3)
Pneumonia	10 (3.8)	3 (2.3)	1 (0.5)	0 (0.0)
Hypertension	9 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	7 (2.7)	0 (0.0)	0 (0.0)	2 (1.3)
General physical health deterioration	6 (2.3)	0 (0.0)	2 (1.0)	0 (0.0)
Dysphagia	3 (1.1)	3 (2.3)	2 (1.0)	1 (0.7)
Dyspnoea	3 (1.1)	5 (3.8)	7 (3.4)	6 (2.9)
Haemoptysis	0 (0.0)	3 (2.3)	0 (0.0)	2 (1.3)
Secondary malignancy	NR	NR	9 (4.3)	4 (1.9)
Pleural effusion	3 (1.1)	1 (0.8)	6 (2.9)	4 (1.9)

NR, not reported.
a SAEs are only reported as treatment-related SAEs for SELECT.
Notes
The majority of individual SAEs reported in both trials were reported by < 2% of patients.
Information drawn from Eisai Ltd[8] and Brose *et al.*,[52] Eisai Ltd's communication with the AG via NICE (2017, personal communication) and Bayer HealthCare's response to the AG's report to the NICE Appraisal Committee (6 September 2017).[157]

TABLE 46 Treatment-related AEs in SELECT and DECISION

Outcome	Study, *n* (%)			
	SELECT		DECISION	
	Lenvatinib (*N* = 261)	Placebo (*N* = 131)	Sorafenib (*N* = 207)	Placebo (*N* = 209)
Treatment-related all-grade AEs	254 (97.3)	78 (59.5)	200 (96.6)	112 (53.6)
Treatment-related grade ≥ 3 AEs	198 (75.9)	13 (9.9)	113 (54.6)	15 (7.2)
Treatment-related SAEs	79 (30.3)	8 (6.1)	26 (12.6)	8 (3.8)
Treatment-related fatal AEs	6 (2.3)	0 (0.0)	1 (0.5)	1 (0.5)

Note
Information drawn from Schlumberger *et al.*[51] and Brose *et al.*[52] [with additional data from the clinical study report for DECISION (table 14.3.3/3)].

TABLE 47 Tumour objective response findings in patients previously treated and not previously treated with VEGFR-targeted therapy in SELECT: first data cut-off point (November 2013)

Outcome	Treatment			
	Prior		No prior	
	Lenvatinib (*n* = 66)	Placebo (*n* = 27)	Sorafenib (*n* = 195)	Placebo (*n* = 104)
ORR (%) (95% CI)	62.1 (50.4 to 73.8)	3.7 (0.0 to 10.8)	65.6 (59.0 to 72.3)	1.0 (0.0 to 2.8)
HR (95% CI)	15.57 (4.06 to 59.72)		58.88 (18.95 to 182.91)	

Note
Information drawn from Schlumberger *et al.*[51] (supplementary appendix, table S4).

Appendix 4 Risk-of-bias assessment of included trials

TABLE 48 Risk-of-bias assessment of SELECT and DECISION

Parameter	Study	
	SELECT	DECISION
Was the method used to assign participants to the treatment groups really random?	✓	✓
Was the allocation of treatment concealed?	✓	✓
Was the number of participants who were randomised stated?	✓	✓
Were details of baseline comparability presented in terms of prognostic factors?	✓	✓
Was baseline comparability achieved in terms of prognostic factors?	✓/✗[a]	✓/✗[a]
Were the eligibility criteria for study entry specified?	✓	✓
Were any co-interventions identified that may influence the outcomes for each group?	✓	✓
Were the outcome assessors blinded to the treatment allocation?	✓	✓
Were the individuals who administered the intervention blinded to the treatment allocation?	✓[b]	✓
Were the participants who received the intervention blinded to the treatment allocation?	✓[c]	✓[d]
Was the success of the blinding procedure assessed?	✗	✗
Were ≥ 80% of the participants originally included in the randomisation process followed up in the final analysis?	✓	✓
Were the reasons for withdrawals stated?	✓	✓
Is there any evidence to suggest that the authors measured more outcomes than they reported?	✓	✓
Was an ITT analysis included?	✓	✓

✗, no (item not properly addressed); ✓, yes (item properly addressed); ✓/✗, partially (item partially addressed).

a In SELECT, median time from diagnosis of DTC to randomisation was shorter in the lenvatinib arm than in the placebo arm (66.0 vs. 73.9 months, respectively). Compared with the placebo arm, a smaller proportion of patients in the lenvatinib arm had metastases in the lung (86.6% vs. 94.7%, respectively) or liver (16.5% vs. 21.4%, respectively). In DECISION, a higher proportion of patients in the sorafenib arm had metastases in the lymph node (54.6%) or pleura (19.3%) than in the placebo arm (48.1% and 11.4%, respectively).

b Study drugs administered by clinicians who remained unaware of the study-drug assignments until the occurrence of unacceptable toxic effects or disease progression as assessed by independent radiologic review.

c If independent radiologic review confirmed disease progression, the patients who were receiving placebo could elect to enter the open-label lenvatinib phase.

d In the event of protocol-defined progression determined by the investigator, treatment could be unmasked and patients from both groups could begin open-label sorafenib and continue until treatment was no longer beneficial, based on investigator judgement.

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Appendix 5 Evidence from systematic reviews

TABLE 49 Summary of the characteristics of the systematic review evidence included

Study and year of publication	Cancer type	Intervention	Number of studies							Note
			All	RR-DTC	Lenvatinib	Sorafenib	RCT	Non-RCT (prospective)	Non-RCT (retrospective)	
Anderson *et al.* 2013[61]	RR-DTC	Potential treatment options for RR-DTC	45	45	1	3	1	44	0	SLR
Gruber and Colevas 2015[33]	RR-DTC	TKIs	18	18	2	6	2	16	0	SLR
Jean *et al.* 2016[93]	DTC vs. other cancer	Sorafenib	9	4	0	4	4	5	0	SLR (PubMed only)
Kawalec *et al.* 2016[97]	RR-DTC	Lenvatinib and sorafenib	2	2	1	1	2	0	0	SR and ITC
McFarland and Misiukiewicz 2014[104]	RR-DTC	Sorafenib (single or in combination)	18	18	0	18	1	12	5	SLR
Shen *et al.* 2014[127]	RR-DTC	Sorafenib	7	7	0	7	0	5	2	SLR
Thomas *et al.* 2014[138]	Metastatic thyroid cancer	Sorafenib	7	6	0	7	0	6	1	SLR
Tremblay *et al.* 2016[57]	RR-DTC	Lenvatinib vs. sorafenib	2	2	1	1	2	0	0	Does not report SLR or SR methodology, but reports ITC and MAIC results
Ye *et al.* 2015[141]	Thyroid cancer	Lenvatinib and sorafenib	10	9	2	8	2	8	0	SR and meta-analysis
CADTH (lenvatinib) 2016[6]	RR-DTC	Lenvatinib	2	2	1	1	2	0	0	Includes only SELECT but reports on ITC from Eisai Ltd[8]
CADTH (sorafenib) 2015[5]	RR-DTC	Sorafenib	1	1	0	1	1	0	0	Includes only DECISION
Eisai Ltd 2017[8]	RR-DTC	Lenvatinib	2	2	1	1	2	0	0	Includes ITC
Bayer HealthCare 2017[7]	RR-DTC	Sorafenib	2	2	1	1	2	0	0	Includes ITC

SLR, systematic literature review; SR, systematic review.

TABLE 50 Quality assessment of systematic review evidence included

Assessment criterion	Study												
	Anderson *et al.* 2013[61]	Gruber and Colevas 2015[33]	Jean *et al.* 2016[93]	Kawalec *et al.* 2016[97]	McFarland and Misiukiewicz 2014[104]	Shen *et al.* 2014[127]	Thomas *et al.* 2014[138]	Trembaly *et al.* 2016[57]	Ye *et al.* 2015[141]	CADTH (lenvatinib) 2016[6]	CADTH (sorafenib) 2015[5]	Eisai Ltd 2017[8]	Bayer HealthCare 2017[7]
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	✓	✓/✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the search strategy adequate and appropriate?	✓	✓	✗[a]	✓	✓	✓	✓	NR	✓	✓	✓	✓	✓
Were preventative steps taken to minimise bias and errors in the study selection process?	✓	NR	NR	✓	✓	✓	NR	NR	✓	✓	✓	✓	✓
Were appropriate criteria used to assess the quality of the primary studies, and were preventative steps taken to minimise bias and errors in the quality assessment process	NR	NR	NR	✗[b]	NR	✗	✗	NR	NR	✓[c]	✓[c]	✓	✓[d]
Were preventative steps taken to minimise bias and errors in the data extraction process?	✓	NR	NR	✓	✓	✓	✓	NR	✓	NR	NR	NR	✓
Were adequate details presented for each of the primary studies?	✓	✓/✗	✓	✓	✓	✓	✓/✗	✓	✓	✓	✓	✓	✓
Were appropriate methods used for data synthesis?	✓	✓	✓	✓	✓	✓/✗[e]	✓/✗[e]	✓	✓/✗[f]	✓	✓	✓	✓
Do the authors' conclusions accurately reflect the evidence that was reviewed?	✓	✓	✓	✓	✓	✓	✓	✓	✓/✗[f]	✓	✓	✓	✓
Was the review published in a peer-reviewed journal?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗
Was the review sponsored by a pharmaceutical company?	✓[g]	✗	✗	✗	✗	✗	✓/✗[g]	✓/✗[h]	✗	✗	✗	✓[h]	✓[g]

✗, no (item not properly addressed); ✓, yes (item properly addressed); ✓/✗, partially (item partially addressed); NR, not reported.

a Only PubMed was searched.
b Used the Jadad scale (not an appropriate assessment tool).
c Results of the assessment were not presented.
d Only DECISION was assessed.
e No investigation of heterogeneity of studies included in meta-analysis.
f Subgroup analyses were conducted based on patients with and without RR-DTC; however, the AG considers that all studies of patients with DTC included a majority of, if not all, patients with RR-DTC.
g Bayer HealthCare.
h Eisai Ltd.

TABLE 51 Overall findings/conclusions recorded by the authors of the included systematic review evidence

Study and year of publication	Analysis	Overall findings/conclusions
Anderson *et al.* 2013[61]	Descriptive analysis	Certain treatments, notably TKIs, have shown promise in Phase II trials, and two Phase III randomised placebo controlled trials (SELECT and DECISION) are ongoing
Gruber and Colevas 2015[33]	Descriptive analysis	The most likely outcome of treatment with a TKI is stable disease. Lenvatinib appears to be the most active agent but is not yet available, with a PFS vs. placebo triple that of sorafenib and a RECIST response rate five times that of sorafenib in the Phase III setting
Jean *et al.* 2016[93]	Descriptive analysis	There is a distinct increase in the rate of occurrence of AEs of sorafenib when used in DTC compared with RCC and HCC. Although many theoretical explanations have been proposed, the exact mechanism for this differential in toxic effects remains unclear
Kawalec *et al.* 2016[97]	Indirect comparison (conducted using the Bucher *et al.*[313] method)	Lenvatinib and sorafenib are drugs with strong evidence on efficacy in treatment of RR-DTC. Based on the currently available clinical data, lenvatinib appeared to be more efficacious then sorafenib in RR-DTC therapy. The safety profiles of the drugs were acceptable and quite comparable. Indirect comparison results should be interpreted with caution because of the differences in trial characteristics
McFarland and Misiukiewicz 2014[104]	Descriptive analysis	Although the data are based primarily on non-randomised Phase II trials and on only one randomised Phase III trial, it has been convincingly shown that sorafenib slows the progression of disease in the majority of cases
Shen *et al.* 2014[127]	Descriptive analysis and meta-analysis	As far as PR and AEs are concerned, the results of this meta-analysis indicate that sorafenib has a modest effect in patients with RR-DTC and the high incidence of AEs associated with this agent may affect the quality of patients' lives
Thomas *et al.* 2014[138]	Descriptive analysis and meta-analysis	ORR from meta-analysis is higher than recently reported in DECISION. The difference could be explained by the study design of DECISION and the challenges that arise from using RECIST criteria. The targeted therapy agents are associated with significant incidence of AEs and a small risk of death. Although there is evidence of efficacy with TKIs, these drugs may diminish quality of life because of significant toxicities; therefore, it is important to assess the need for treatment. Most patients with metastatic disease do not require systemic therapy
Tremblay *et al.* 2016[57]	Indirect comparison (conducted using the Bucher *et al.*[313] method) and MAIC	Based on a MAIC of individual patient data from SELECT and aggregate data from DECISION, lenvatinib was associated with statistically significantly longer PFS compared with sorafenib. However, only patient characteristics common to both trials that were reported in DECISION could be matched. The results may therefore have been influenced by other unobserved factors. The conclusions are limited to patients not previously treated with a VEGFR-targeted therapy as these were excluded from the analysis
Ye *et al.* 2015[141]	Descriptive analysis and meta-analysis	Lenvatinib and sorafenib are useful in the treatment of TC. Although their toxicities remain high (57.4%) in the patients, the death rate is controlled (4.1%). Lenvatinib and sorafenib are more useful for thyroid cancer compared with RR-DTC

TABLE 51 Overall findings/conclusions recorded by the authors of the included systematic review evidence (*continued*)

Study and year of publication	Analysis	Overall findings/conclusions
CADTH (lenvatinib) 2016[6]	Descriptive analysis[a]	The Endocrine Clinical Guidance Panel concluded that there is a net overall clinical benefit of lenvatinib in the treatment of RR-DTC. In making this conclusion, the Clinical Guidance Panel also noted that OS was a secondary end point and confounded by crossover; HRQoL was not studied but AE profiles were similar to AEs seen with sorafenib in DECISION. Hypertension was more common with lenvatinib but hand-foot syndrome and drug discontinuation owing to AEs was more common with sorafenib
CADTH (sorafenib) 2015[5]	Descriptive analysis	The Endocrine Clinical Guidance Panel concluded that there is a net overall clinical benefit of sorafenib compared with placebo in patients with clinically progressive RR-DTC. Toxicity was increased with sorafenib compared both with placebo and with other trials studying sorafenib in cancer, and there may be an increased risk of squamous cell cancers of the skin during sorafenib use. As HRQoL was reduced by sorafenib, the decision to initiate treatment and the monitoring of treatment should be by a clinician experienced in the use of targeted agents and in the treatment of thyroid cancer
Eisai Ltd 2017[8]	Descriptive analysis and indirect comparison (conducted using the Bucher *et al.*[313] method)	Lenvatinib was shown to be of superior efficacy to placebo in SELECT (crossover-adjusted OS, PFS and ORR) and to sorafenib (PFS) from an ITC. Comparative safety information with sorafenib has shown that sorafenib and lenvatinib share many of their AEs, although their safety profiles are not identical and lenvatinib is associated with lower rates of some AEs that have been shown to impact patients' daily lives
Bayer HealthCare 2017[7]	Descriptive analysis and indirect comparison (conducted using the Bucher *et al.*[313] method) and MAIC	Crossover makes it difficult to detect and attribute improvements in OS in DECISION. Although there were no statistically significant differences between arms, analyses of OS, at 9 months and 36 months after the original data cut-off point, showed a consistent separation of the K–M curves in favour of sorafenib. Results from the indirect comparison show the safety profile of sorafenib to be statistically superior to that of lenvatinib with respect to AEs. Overall, AEs in DECISION were consistent with the known safety profile of sorafenib in other indications, and effectively managed by supportive care, pharmacological treatment, dose interruption or dose reduction. In addition, sorafenib was shown to be associated with a lower risk of treatment discontinuation attributable to AEs. Sorafenib is an efficacious treatment option, especially for patients presenting with comorbidities or in circumstances in which managing and maintaining quality of life is a primary treatment objective. The results of DECISION are directly relevant to the progressive RR-DTC patients within routine clinical practice in England. The safety results from the indirect comparison support sorafenib as a tolerable treatment option. This may be important in patients with comorbidities in whom managing and maintaining quality of life is a primary treatment objective. Please note that Bayer HealthCare has since clarified that it considers indirect comparison results to be unreliable owing to important differences between SELECT and DECISION (communication with the AG via NICE, 2017, personal communication)

PR, partial response.

a The CADTH did not include an indirect comparison of lenvatinib with sorafenib as part of the evidence summarised as part of its systematic review. It did however note that the manufacturer had submitted a MAIC to compare lenvatinib with sorafenib and these results were also presented.

TABLE 52 Results from three systematic reviews of sorafenib

Outcome	Systematic review				
	Jean *et al.* 2016[93]			Shen *et al.* 2014[127] (95% CI)	Thomas *et al.* 2014[138] (95% CI)
	TARGET trial (RCC)[314]	SHARP trial (HCC)[315]	DECISION	Meta-analysis[a]	Meta-analysis[a]
Efficacy					
PFS (months)	5.5[b]	5.5[b,c]	10.8	–	17.9 (17.9 to 18.0)[d]
ORR (%)	1.6[b]	0.7[b]	12.2[b]	22 (15 to 28)	20.9 (14.3 to 27.5)[d]
All-grade AEs (%)					
Hand–foot syndrome	30[b]	21[b]	76[b]	80 (68 to 91)	73.5 (64 to 83)
Rash	40[b]	16[b]	50[b]	66 (50 to 82)	66.7 (51.7 to 81.7)
Diarrhoea	43[b]	39[b]	69[b]	68 (59 to 77)	70.3 (62.3 to 78.3)
Hypertension	17[b]	5[b]	41[b]	52 (33 to 72)	36.1 (26.6 to 45.6)
Fatigue	37[b]	22[b]	50[b]	67 (57 to 78)	60.6 (44.8 to 76.4)
Weight loss	10[b]	9[b]	51[b]	52 (33 to 72)	56.8 (38.8 to 74.8)
Mucositis	NR	NR	36[b]	–	35.4 (23.1 to 47.7)
Grade ≥ 3 AEs (%)					
Hand–foot syndrome	6	8	20	–	19.4 (8.3 to 30.5)
Rash	1	1	5	–	6.8 (2.7 to 10.9)
Diarrhoea	2	8	6	–	6.8 (3.3 to 10.3)
Hypertension	4	2	10	–	7.3 (2.5 to 12.1)
Fatigue	5	4	6	–	10.3 (4.4 to 16.2)
Weight loss	< 1[b]	2[b]	12[b]	–	5.2 (1.2 to 90.2)
Mucositis	NR	NR	4[b]	–	3.9 (0.6 to 7.2)
Dose modifications owing to AEs (%)					
Dose reductions	13[b]	26[b]	64[b]	62 (36 to 89)	56 (43.4 to 69.3)
Discontinued	10[b]	38[b]	19[b]	–	16 (8.6 to 23.4)

NR, not reported; SHARP, Sovafenib Hepatocellular Carcinoma Assessment Randomised Protocol; TARGET, Treatment Approaches in Renal Cancer Global Evaluation Trial.

a The meta-analyses in both reviews included seven studies (six studies for RR-DTC only in the review by Thomas *et al.*[138]).

b Data not reported in the review by Jean *et al.*[93] or did not match the data reported in the source papers and so data were extracted by the AG from source papers.[52,314,315]

c The SHARP trial[315] reports time to symptomatic progression (median of 4.1 months) and time to radiological progression (median of 5.5 months); the latter is reported here.

d PFS includes patients with medullary thyroid cancer. From all studies, including the study of patients with medullary thyroid cancer, median ORR was 20.7% (95% CI 13.0% to 28.0%).

TABLE 53 Efficacy results from indirect comparisons: lenvatinib vs. sorafenib

Outcome	Relative effectiveness	Source
OS (RPSFTM adjusted)	HR 0.78 (95% CI 0.42 to 1.42)	Kawalec *et al.* 2016[97]
OS (RPSFTM adjusted)	HR 0.77 (95% CI 0.44 to 1.35)	Tremblay *et al.* 2015[289]
OS (RPSFTM adjusted)	Academic in confidence[a]	Eisai Ltd 2017[8]
OS (MAIC and RPSFTM adjusted)	HR 0.73 (95% CI 0.40 to 1.35)	Tremblay *et al.* 2015[289]
PFS	HR 0.36 (95% CI 0.22 to 0.57)	Kawalec *et al.* 2016[97]
PFS	HR 0.36 (95% CI 0.22 to 0.57)	Tremblay *et al.* 2015[289]
PFS	Academic in confidence[a]	Eisai Ltd 2017[8]
PFS (MAIC-adjusted)	HR 0.33 (95% CI 0.22 to 0.57)	Tremblay *et al.* 2015[289]

MAIC, Matching-Adjusted Indirect Comparison.
a It is anticipated that the data will be published in April 2018 (Eisai Ltd's communication with the AG via NICE, 2017, personal communication).

TABLE 54 Efficacy results from indirect comparisons: sorafenib vs. lenvatinib

Outcome	Relative effectiveness	Source
OS (MAIC and RPSFTM adjusted)	Academic in confidence[a]	[b]Tremblay *et al.* 2015[289]
OS (MAIC and RPSFTM adjusted)	Academic in confidence[a]	Bayer HealthCare 2017[7]
PFS (MAIC adjusted)	Academic in confidence[a]	[b]Tremblay *et al.* 2015[289]
PFS (MAIC adjusted)	Academic in confidence[a]	Bayer HealthCare 2017[7]

MAIC, Matching-Adjusted Indirect Comparison.
a Bayer HealthCare considers that the data from this analysis are unreliable owing to important differences between SELECT and DECISION and therefore do not wish the results to be presented (communication with the AG via NICE, 2017, personal communication).
b Direction of analysis inverted from publication, as reported in Bayer HealthCare[7] (*Table 19*).

TABLE 55 Safety results from indirect comparisons

	Comparison	
Outcome	Lenvatinib vs. sorafenib (Kawalec *et al.* 2016[97]), HR (95% CI)	Sorafenib vs. lenvatinib (Bayer HealthCare 2017[7]), HR (95% CI)
Grade ≥ 3 AE	NR	Academic in confidence[a]
SAE	1.54 (0.99 to 2.40)	Academic in confidence[a]
Treatment-related SAE	4.02 (1.69 to 9.60)	Academic in confidence[a]
Discontinuation owing to AE	1.26 (0.32 to 4.96)	Academic in confidence[a]

NR, not reported.
a Bayer HealthCare considers that the data from this analysis are unreliable given important differences between SELECT and DECISION and therefore do not wish the results to be presented (communication with the AG via NICE, 2017, personal communication).

Note
Data are also reported for 17 specific types of AEs by Kawalec *et al.*[97] The difference between lenvatinib and sorafenib was statistically significant for hypertension (HR 2.31, 95% CI 1.18 to 4.53) and alopecia (HR 0.33, 95% CI 0.12 to 0.94).

Appendix 6 Proportional hazards assumption

The AG assessed the validity of the PH assumptions in DECISION and SELECT.

The H–H (cumulative hazard vs. cumulative hazard) plot for PFS by investigator assessment from SELECT (final data cut-off point) is provided in *Figure 22*. The estimated constant for a linear relationship is statistically significantly different from zero (–0.0589, 95% CI –0.075 to –0.043; $p = 6.73$ E-12). Comparison by analysis of variance (ANOVA) of the linear trend with a quadratic trend shows an improved fit [$F(146,1) = 252.3$; $p = 1.25$ E-33], indicating that the assumption of PH does not hold for investigator-assessed PFS data from SELECT.

The H–H plot for OS unadjusted for treatment crossover from SELECT (final data cut-off point) is provided in *Figure 23*. The estimated constant for a linear relationship is statistically significantly different from zero (–0.0103, 95% CI –0.0200 to –0.00005; $p = 0.039$). Comparison by ANOVA of the linear trend with a

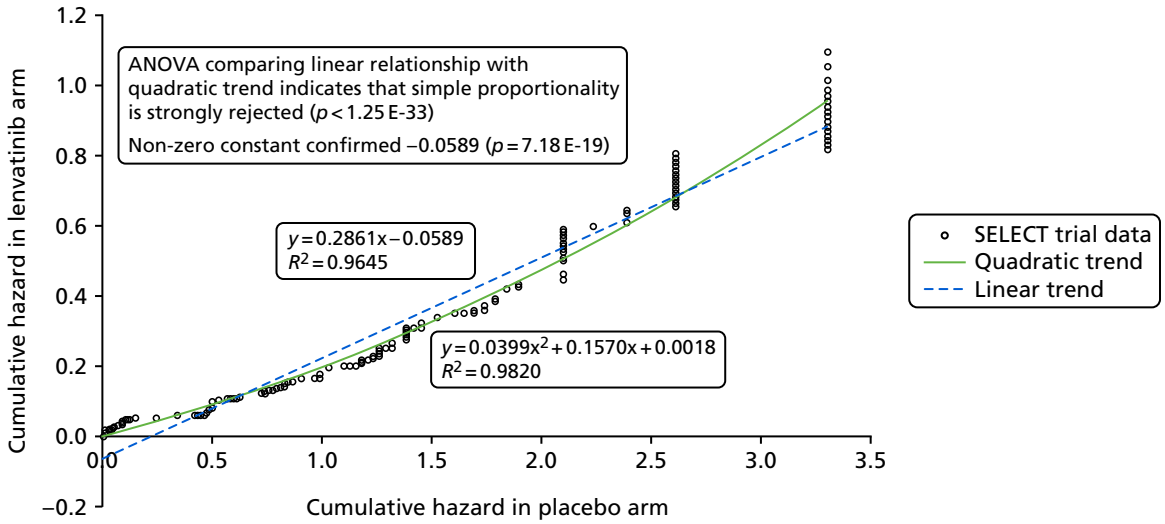

FIGURE 22 The H–H plot for PFS data from SELECT.

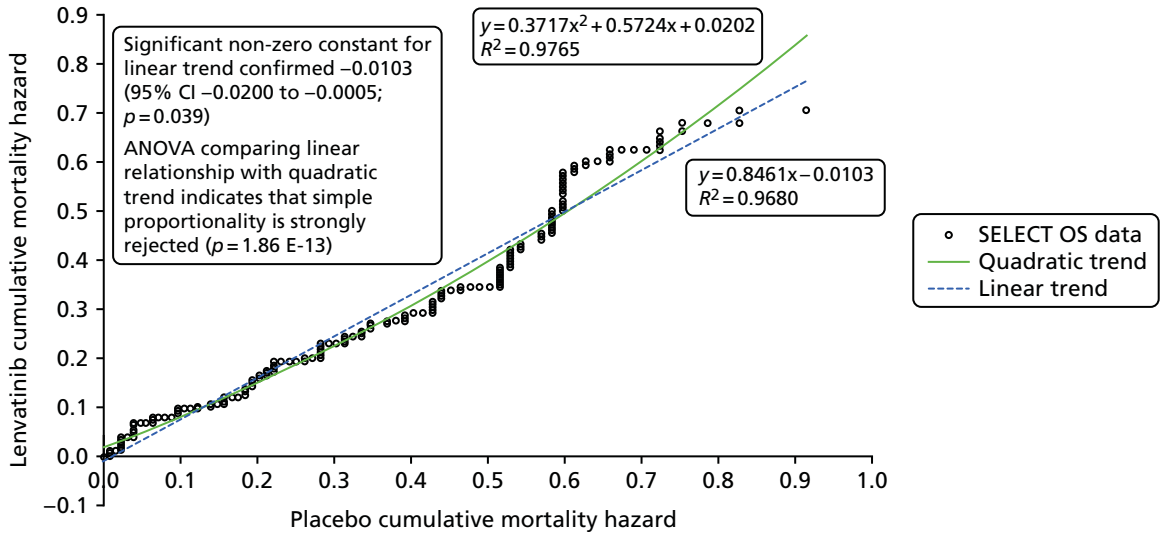

FIGURE 23 The H–H plot for unadjusted OS data from SELECT.

quadratic trend shows a significantly improved fit for the quadratic relationship [$F(146,1) = 63.6$; $p = 1.86$ E-13), indicating that the assumption of PH does not hold for unadjusted OS data from SELECT.

The H–H plot for OS adjusted by RPSFTM for treatment crossover using data from SELECT (final data cut-off point) is provided in *Figure 24*. In this case, the estimated constant for the fitted linear trend does not show a significant deviation from zero (–0.0041, 95% CI –0.0166 to 0.0084; $p = 0.52$). However, a comparison by ANOVA of the linear trend with a fitted quadratic trend shows an improved fit for the quadratic relationship [$F(166,1) = 12.03$; $p = 0.000665$], indicating that the assumption of PH is questionable on the basis of evidence of non-linearity in the relationship between the two arms of the trial following adjustment for crossover.

The linear trend fitted to the PFS DECISION data (final data cut-off point) in *Figure 25* shows a statistically significant non-zero constant of –0.1263 (95% CI –0.1635 to –0.0892; $p = 2.59$ E-10). In addition, the ANOVA test for non-linearity indicates a statistically significant deviation from linearity [$F(177,1) = 6.722$; $p = 0.0103$]. On both criteria, the PH assumption is called into question.

The linear trend fitted to the unadjusted OS data from the DECISION trial (final data cut), shown in *Figure 26*, shows a very small constant of 0.0018 (95% CI –0.0036 to 0.0073; $p = 0.505$), consistent with the PH requirement for a zero constant. In addition, the ANOVA test for non-linearity indicates no statistically significant deviation from linearity [$F(89,1) = 0.0675$; $p = 0.796$]. On both criteria, the PH assumption is supported for unadjusted OS trial data.

Figure 27 shows the linear trend fitted to the RPFST-adjusted OS DECISION data (final data cut-off point), which shows a statistically significant non-zero constant of 0.0115 (95% CI 0.0026 to 0.0204; $p = 0.0117$). In addition, the ANOVA test for non-linearity indicates a statistically significant deviation from linearity [$F(122,1) = 56.915$; $p = 9.03$ E-12]. On both criteria, the PH assumption is questionable.

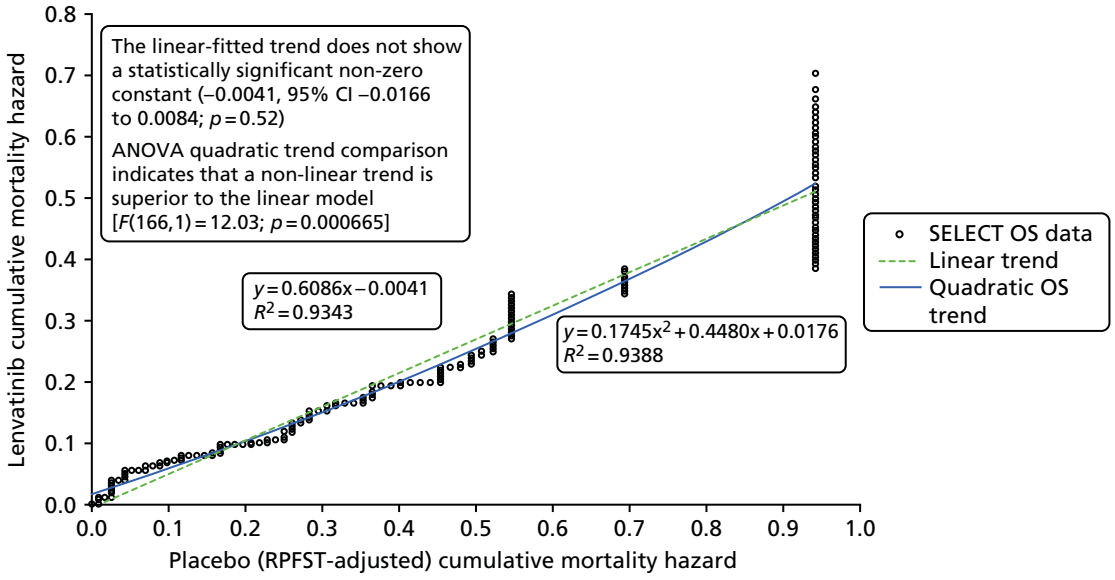

FIGURE 24 The H–H plot for OS data adjusted by RPFST for treatment crossover from SELECT.

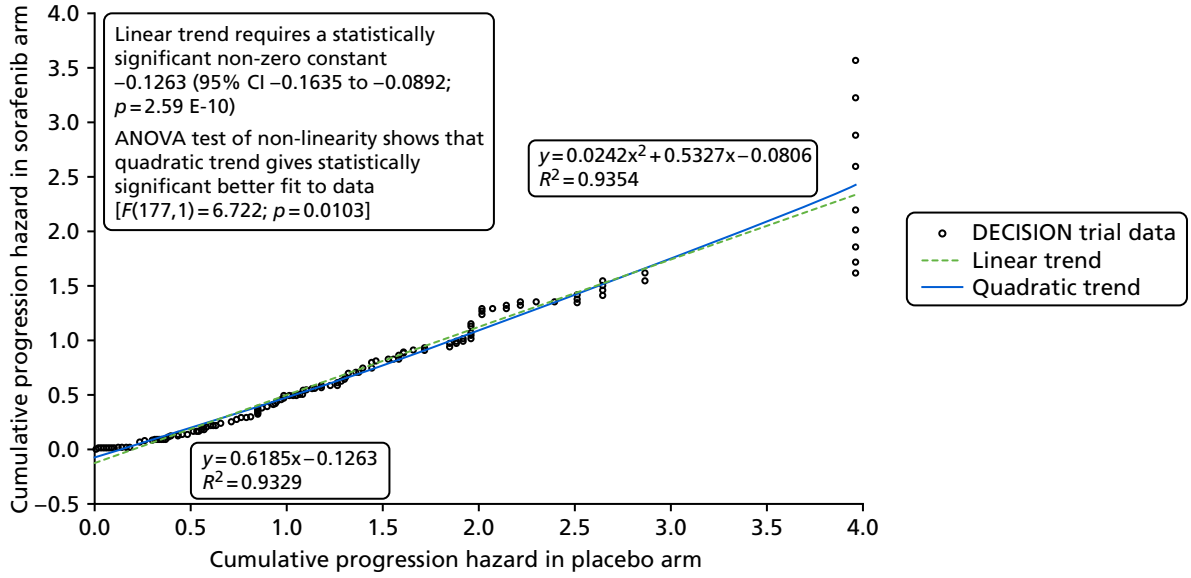

FIGURE 25 The H–H plot for PFS from DECISION.

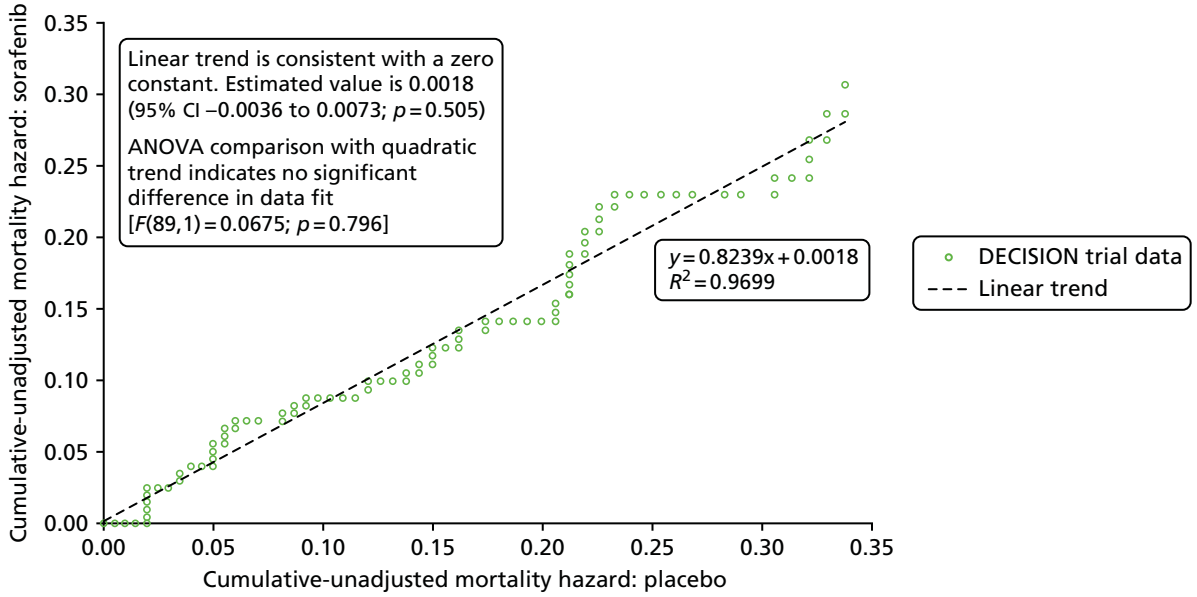

FIGURE 26 The H–H plot for unadjusted OS data from DECISION.

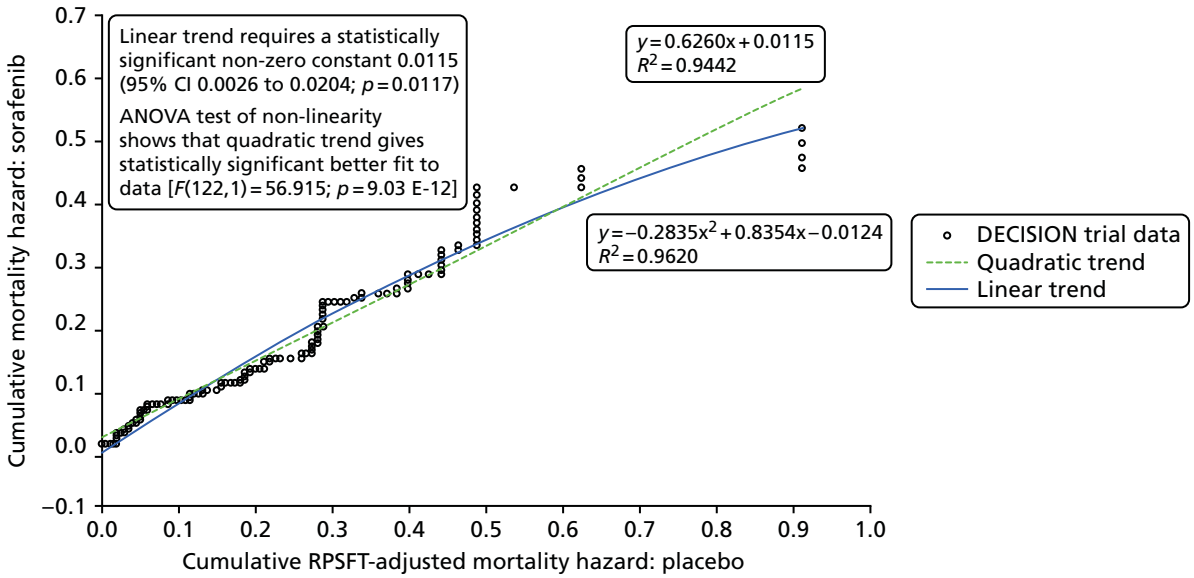

FIGURE 27 The H–H plot for RPFST-adjusted OS from DECISION.

Appendix 7 Data extraction tables from extended open-label phases of the trials not presented in the main body of the report

TABLE 56 Efficacy analyses from the non-randomised extended open-label phase of SELECT and DECISION

	Study				
	SELECT			DECISION	
Outcome	Lenvatinib: 24-mg dose ($n = 85$)	Lenvatinib: 20-mg dose ($n = 30$)	Lenvatinib: either dose ($n = 115$)	Sorafenib after sorafenib ($n = 46$)	Sorafenib after placebo ($n = 137$)
Data cut-off point	Second data cut-off point: June 2014			First data cut-off point: August 2012	
OS	NR	NR	NR	NR	NR
Median PFS (months) (95% CI)	17.5 (8.3 to NE)	NE (10.9 to NE)	22.1 (9.4 to NE)	6.7	9.6
ORR (%) (95% CI)	52.9 (41.8 to 63.9)	60.0 (40.6 to 77.3)	54.8 (45.2 to 64.1)	12.2	9.5

NE, not estimable; NR, not reported.

Notes

Results are reported from the start of the open-label treatment.

Information drawn from the EMA,[26,27] Schlumberger *et al.*[122] and Paschke *et al.*[114]

TABLE 57 Safety analyses from the non-randomised extended open-label phase of SELECT and DECISION

	Study	
	SELECT	DECISION
Parameter	Lenvatinib: 24-mg dose ($n = 82$)	Sorafenib after placebo ($n = 150$)
Data cut-off point	First data cut-off point: November 2013	First data cut-off point: August 2012
Median duration of treatment (months) (range)	8.9 (0–25)	13.1[a]
Median dose intensity (mg) (range)	19.4 (7–24)	NR
Dose reductions owing to AEs (%)	43.9	NR
Dose interruptions owing to AEs (%)	70.7	NR
Treatment-related AEs (%)	85.4	NR
Common AEs (%)[b]		
Hypertension	54	28.7
Diarrhoea	52	56.0
Decreased appetite	43	25.3
Weight loss	39	41.3
Fatigue	38	24.7

continued

TABLE 57 Safety analyses from the non-randomised extended open-label phase of SELECT and DECISION (*continued*)

Parameter	Study	
	SELECT	DECISION
	Lenvatinib: 24-mg dose ($n = 82$)	Sorafenib after placebo ($n = 150$)
Hand–foot syndrome	NR	56.7
Alopecia	NR	56.7
Rash	NR	29.3
Common grade ≥ 3 AEs (%)[b]		
Hypertension	24	NR
Weight loss	9	NR
Proteinuria	7	NR
Asthenia	6	NR
Fatigue	6	NR
Treatment-related fatal AEs (%)	4.9	NR

NR, not reported.
a Reported as 56.9 weeks, converted to months by dividing by 4.34812141.
b AEs are reported to be treatment related for SELECT and treatment emergent for DECISION.
Notes
Results are reported from the start of the open-label treatment.
Information drawn from Robinson *et al.*[118] and Bayer HealthCare.[7]

Appendix 8 Evidence from observational studies

TABLE 58 Study characteristics of observational studies

	Observational study								
Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen *et al.*	Duntas *et al.*	Kloos *et al.*	Study 12791	Marotta *et al.*
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31	RR-DTC: 17
Primary source	Cabanillas *et al.* 2015[77]	Takahashi *et al.* 2016[135] (abstract)	Ahmed *et al.* 2011[59]	Gupta-Abramson *et al.* 2008[88]	Chen 2011[78] (abstract)	Duntas *et al.* 2011[81] (abstract)	Kloos *et al.* 2009[101]	Schneider *et al.* 2012[126]	Marotta *et al.* 2016[103]
Other sources	Two abstracts[128,129] and lenvatinib EPAR[27]	One other abstract[136] and lenvatinib EPAR[27]	One other abstract[60] and lenvatinib EPAR[27]	Five abstracts[75,76,80,98,137]	None	None	Lenvatinib EPAR[27]	One abstract[125] and one other study[92]	None
Country	USA, Italy, UK, Australia, Poland and France	Japan	UK	USA	China	Greece	USA	The Netherlands	Italy
Recruitment period	October 2008 to February 2010	3 September 2012 to 9 July 2015, latest cut-off date[a]	Patient accrual commenced in May 2007	February 2006 to August 2009	NR	NR	October 2004 and August 2005	October 2007 and February 2011	NR
Length of follow-up	September 2013: median 16.1 months (range 15.0–16.6 months) June 2014: median 51.6 months	Safety: 2 years Secondary outcomes: 40 months[a]	Median 19 months	[b,c]Median 9 months[75]	Minimum 3 months[b]	4 to 9 months	NR	Median 25 months (range 3.5–39 months)	Median 17 months

NR, not reported.

a Data taken from lenvatinib EPAR.[27]

b Converted from weeks into months by dividing by 4.34812141.

c This was the median length of follow-up reported for an interim analysis presented by Brose *et al.*;[75] final results have been presented at later dates[98,137] and so the median follow-up is likely to be longer than reported here.

TABLE 59 Participant characteristics of observational studies

	Observational study								
Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen *et al.*	Duntas *et al.*	Kloos *et al.*	Study 12791	Marotta *et al.*
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31	RR-DTC: 17
Median age (years) (range)	63 (34–77)	NR	All: 55 (21–78)	Initial 30 patients: 63 (31–89)	NR	NR	PTC/no prior chemotherapy ($n = 19$): 67 (33–90) PTC/prior chemotherapy ($n = 22$): 56 (27–75)	Median 64 (53–82)	58
% male	59	NR	All: 55.9	All: 49.0[75]	NR	36.4	All: 55.4 PTC ($n = 41$): 51.2	61.2	23.5
Race (%)	White: 86	NR	NR	NR	NR	NR	White • All: 83.9 • PTC ($n = 41$): 87.8	NR	NR
ECOG PS ≥ 2 (%)	6.9	NR	All: 0	Initial 30 patients: 0	NR	NR	NR	NR	35.3
PTC (%)	74.1	NR	All: 23.5	All: 52.7	100	NR	73.2	41.9	35.3
FTC (%)	25.9[a]	NR	All: 14.7	32.7[a]	0	NR	19.6[a]	48.4	64.7
Lung metastases (%)	93	NR	NR	NR	NR	NR	NR	Lung only: 25.8	NR
Bone metastases (%)	45	NR	NR	NR	NR	NR	NR	Lung and bone only: 25.8	23.5
Prior TKI	29.3	NR	NR	NR	NR	NR	NR	0	11.8

ATC, anaplastic thyroid carcinoma; FTC, follicular carcinoma; MTC, medullary thyroid carcinoma; NR, not reported.
a Explicitly stated that FTC also includes Hürthle cell carcinoma.

TABLE 60 Efficacy findings from observational studies

	Observational study								
Parameter	**Study 201**	**Study 208**	**Study 12636**	**UPCC-03305**[a]	**Chen *et al.***	**Duntas *et al.***	**Kloos *et al.***	**Study 12791**	**Marotta *et al.***
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31	RR-DTC: 17
Median OS (months) (95% CI)	September 2013: 27.7 (27.7 to NE)[b] June 2014: 32.3 (23.3 to 35.8)[b]	RR-DTC only: 31.8 (31.8 to NE)[b]	RR-DTC only: median not met	RR-DTC: 32.4 (21.6 to NE)[c]	NR	NR	23 (18 to 43)[d]	34.5 (19 to 50) ($n = 26$)	No patient died during follow-up
Median PFS (months) (95% CI)	12.6 (9.9 to 16.1)	RR-DTC only: 25.8 (18.4 to NE)	RR-DTC only: median not met	RR-DTC only: 22.1 (17.3 to 31.1)[c]	Mean: 9.7 (6.8 to 12.4)[c]	NR	All PTC ($n = 41$): 15 (10 to 27.5)	18 (7 to 29) ($n = 26$)	12
ORR (%) (95% CI)	50.0 (36.6 to 63.4)	RR-DTC only: 68.0	21[d]	RR-DTC only: 38.3	33.3	27.3	All PTC ($n = 41$): 15[d]	30.8 ($n = 26$)	35.3
Median time to response (months)	3.6 (95% CI 1.8 to 3.7)	NR	NR	NR	NR	NR	NR	All responses achieved in the first 6 months of treatment ($n = 26$)	NR
Duration of response (months)	12.7 (8.8 to NE) ($n = 29$)	NR	NR	NR	NR	NR	NR for all PTC patients	29.6 (range 3–33) ($n = 26$)	NR

ATC, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma; NE, not estimable; NR, not reported.
a Findings are from Keefe *et al.*[98]
b Data taken from lenvatinib EPAR.[27]
c Converted from weeks into months by dividing by 4.34812141.
d Data taken from sorafenib EPAR.[26]
Note
ORR = complete response + partial response; there were no patients with a complete response in any of the studies.

TABLE 61 All-grade AEs reported in the prospective observational studies

Event	Prospective observational study		
	Lenvatinib, two studies,[77,135] treatment emergent (%)	Sorafenib, four studies,[59,78,81,126] treatment emergent (%)	Sorafenib, two studies,[88,101] treatment related (%)
All-grade AEs	100[a]	NR	NR
Hypertension	76 to 90[a]	21 to 42[c]	43[a]
Diarrhoea	55 to 67[a]	52 to 77[c]	75 to 80[a]
Decreased appetite	52 to 78[a]	29[b]	20 to 82[a]
Weight loss	69[b]	29 to 58[a]	60 to 82[a]
Nausea	50[b]	10 to 27[a]	30 to 55[a]
Fatigue	60 to 73[a]	59[b]	63 to 66[a]
Headache	43[b]	15[b]	16[b]
Stomatitis/ mucositis	31 to 57[a]	27 to 48[c]	16 to 47[a]
Vomiting	38[a]	18[b]	18[b]
Proteinuria	61 to 64[a]	NR	NR
Hand–foot syndrome	22 to 77[a]	71 to 79[c]	63 to 93[a]/63 to 91[a,d]
Dysphonia	43[b]	NR	NR
Rash	24[b]	55 to 88[a]	79 to 80[a]/79 to 85[a,d]
Alopecia	9[b]	52 to 74[a]	43 to 79[a]
Other types of all-grade AEs	Other AEs experienced by ≥ 25% of patients in Study 201[77] (Study 208[135] only reported AEs that were experienced by ≥ 55% of patients): • Cough, 45 • Arthralgia, 36 • Dry mouth, 35 • Back pain, 33 • Pain in extremity, 33 • Dyspnoea, 31 • Musculoskeletal pain, 31 • Abdominal pain upper, 31 • Abdominal pain, 28 • Epistaxis, 28	Other AEs experienced by ≥ 25% of patients in any one study:[59,126] • Infection, 68 • Hypocalcaemia, 48 • Abdominal cramps/pain, 38 • Glossitis, 35 • Hypophosphataemia, 35 • Anaemia, 35 • Hypoparathyroidism, 32 • Thrombopenia, 29 • Haemorrhage, 29 • Hypothyroidism, 26 • Leukopenia, 23 • Myocardial infarction, 10	Other treatment-related AEs experienced by ≥ 25% of patients in Kloos *et al.* 2009:[101] • Dry skin, 84 • Pruritis, 77 • Flatulence, 70 • Arthralgia, 61 • Pain abdomen or rectal, 68 • Heartburn, 39 • Muscle cramps, 36 • Flushing, 32 • Nail changes, 59

NR, not reported.
a Range of AE incidence reported by two studies.
b Incidence of AEs reported by one study.
c Range of AE incidence reported across three studies.
d Terry *et al.*[137] later examined treatment-related hand–foot syndrome and rash for UPCC-03305 (12192)[88] and data in the table are reported as ranges using earlier and later data cut-off points, respectively.

TABLE 62 Incidence of all-grade AEs reported from observational studies

	Observational study							
	n (%)							
Parameter	Study 201	Study 208	Study 12636	UPCC-03305[a,b]	Chen *et al.*	Duntas *et al.*	Kloos *et al.*[a]	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
All-grade AEs	58 (100)	51 (100)	NR	NR	NR	NR	NR	NR
Hypertension	44 (76)	46 (90)	7 (21)	13 (43)	NR	3 (27)	24 (43)	13 (42)
Diarrhoea	39 (67)	28 (55)	26 (77)	24 (80)	NR	One of the most frequent AEs[c]	42 (75)	16 (52)
Decreased appetite/anorexia	30 (52)	40 (78)	10 (29)	6 (20)	NR	NR	46 (82)	NR
Weight loss	40 (69)	NR	10 (29)	18 (60)	NR	NR	46 (82)	18 (58)
Nausea	29 (50)	NR	9 (27)	9 (30)	NR	NR	31 (55)	3 (10)
Fatigue	35 (60)	37 (73)	20 (59)	19 (63)	NR	One of the most frequent AEs[c]	37 (66)	NR
Headache	25 (43)	NR	5 (15)	NR	NR	NR	9 (16)	NR
Stomatitis/mucositis	18 (31)	29 (57)	9 (27)	14 (47)	NR	NR	9 (16)	15 (48)
Vomiting	22 (38)	NR	6 (18)	Included with nausea	NR	NR	10 (18)	NR
Proteinuria	37 (64)	31 (61)	NR	NR	NR	NR	NR	NR
Hand–foot syndrome	13 (22)	39 (77)	27 (79)	28 (93)	NR	One of the most frequent AEs[c]	35 (63)	22 (71)
Dysphonia	25 (43)	NR	NR	NR	NR	NR	NR	NR
Rash	14 (24)	NR	Dermatology (other): 30 (88)	24 (80)	NR	NR	44 (79)	17 (55)
Alopecia	5 (9)	NR	25 (74)	13 (43)	NR	NR	44 (79)	16 (52)

	Observational study							
	n (%)							
Parameter	Study 201	Study 208	Study 12636	UPCC-03305[a,b]	Chen *et al.*	Duntas *et al.*	Kloos *et al.*[a]	Study 12791
Other types of all-grade AEs	Other AEs experienced by ≥ 25% of patients: • Cough, 26 (45) • Arthralgia, 21 (36) • Dry mouth, 20 (35) • Back pain, 19 (33) • Pain in extremity, 19 (33) • Dyspnoea, 18 (31) • Musculoskeletal pain, 18 (31) • Abdominal pain upper, 18 (31) • Abdominal pain, 16 (28) • Epistaxis, 16 (28)	None; note that abstract only reports AEs reported by ≥ 55% of patients	Other AEs experienced by ≥ 25% of patients: • Infection, 23 (68) • Abdominal cramps/pain, 13 (38) • Glossitis, 12 (35) • Haemorrhage, 10 (29)	Terry *et al.* 2013[137] later examined treatment-related hand–foot syndrome and rash. AE data for all 55 patients not RR-DTC only ($n = 47$): • Hand–foot syndrome, 50 (91) • Rash, 49 (85)	NR	NR	Other AEs experienced by ≥ 25% of patients: • Pain abdomen or rectal, 35 (63) • Heartburn, 22 (39) • Flatulence, 39 (70) • Arthralgia, 34 (61) • Muscle cramps, 20 (36) • Flushing, 64 • Dry skin, 47 • Pruritis, 43 • Nail changes, 33	• Hypocalcaemia, 15 (48) • Hypophosphataemia, 11 (35) • Anaemia, 11 (35) • Hypoparathyroidism, 10 (32) • Thrombopenia, 9 (29) • Hypothyroidism, 8 (26) • Leukopenia, 7 (23) • Myocardial infarction, 3 (10)

ATC, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma; NR, not reported.
a Treatment-related.
b The majority of findings are from Terry *et al.*[137]
c Duntas *et al.*[81] report that 'The most frequently reported side effects were hand-foot syndrome, fatigue, diarrhoea and, in three patients, arterial hypertension'.

TABLE 63 Grade ≥ 3, serious and fatal AEs reported in the prospective observational studies

Event	Prospective observational study (%)		
	Lenvatinib, two studies,[77,135] treatment emergent	Sorafenib, four studies,[59,78,81,126] treatment emergent	Sorafenib, two studies,[88,101] treatment related
Grade ≥ 3 AEs	72[a]	NR	NR
Hypertension	10[b]	6 to 16[a]	4 to 13[a]
Diarrhoea	10[b]	3 to 7[a]	4 to 7[a]
Decreased appetite	2[b]	0[b]	3[b]
Weight loss	12[b]	0 to 10[a]	5 to 10[a]
Nausea	0[b]	0[a]	0[a]
Fatigue	9[b]	9[a]	3 to 16[a]
Headache	2[b]	3[b]	0[b]
Stomatitis/mucositis	2[b]	9 to 10[a]	0 to 2
Hand–foot syndrome	2[b]	23 to 44[a]	7 to 10[a]/7[a,c]
Proteinuria	10[b]	NR	NR
Asthenia	NR	NR	NR
Dyspnoea	0[b]	NR	0[b]
Dysphagia	NR	0[b]	NR
Rash	0[b]	6 to 16[a]	4 to 10[a]/4 to 18[a,c]
Other types of grade ≥ 3 AEs	Other grade ≥ 3 AEs experienced by ≥ 5% of patients in Study 201: • Dehydration, 9 • Arthralgia, 5 • Grade ≥ 3 AEs not reported in Study 208	Other grade ≥ 3 AEs experienced by ≥ 5% of patients in any one of the studies: • Myocardial infarction, 10 • Infection, 9 • Arthralgia, 9 • Drug hypersensitivity, 9	Other grade ≥ 3 treatment-related AEs experienced by ≥ 5% of patients in either study: • Hand or foot pain, 12 • Arthralgia, 11 • Fatigue, 16 • Hand–foot syndrome, 7 • Musculoskeletal chest pain, 7 • Asymptomatic hyponatraemia, 5 • Function tests, 7 • Pruritus, 3 • Sleep disturbance/anxiety, 3
SAEs	48[b]	NR	NR
Fatal AEs	5 to 8[a]	1[b]	NR
Type of SAEs	SAEs that occurred in ≥ 3.5% of patients in Study 201: • Dehydration, 7 • Hypotension, 5 • Pulmonary embolism, 3 • Abdominal pain, 3 • Hypertension, 3 • Cardiac failure, 3	NR	NR

NR, not reported.
a Range of AE incidence reported by two studies.
b Incidence of AEs reported by one study.
c Terry *et al.*[137] later examined treatment–related hand–foot syndrome and rash for UPCC-03305 (12192)[88] and data in the table are reported as ranges using earlier and later data cut-off points, respectively.

TABLE 64 Incidence of grade ≥ 3 AEs reported from observational studies

	Observational study, *n* (%)							
Parameter	Study 201	Study 208	Study 12636	UPCC-03305[a]	Chen *et al.*	Duntas *et al.*	Kloos *et al.*[a]	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
Grade ≥ 3 AEs	42 (72)	RR-DTC: 12 (72)	NR	NR	NR – see 'other'	NR	NR	NR
Hypertension	6 (10)	NR	2 (6)	4 (13)	NR	NR	2 (4)	5 (16)
Diarrhoea	6 (10)	NR	1 (3)	2 (7)	NR	NR	2 (4)	2 (7)
Decreased appetite	1 (2)	NR	0	1 (3)	NR	NR	0	NR
Weight loss	7 (12)	NR	0	3 (10)	NR	NR	3 (5)	3 (10)
Nausea	0	NR	0	0	NR	NR	0	0
Fatigue	5 (9)	NR	3 (9)	1 (3)	NR	NR	9 (16)	NR
Headache	1 (2)	NR	1 (3)	NR	NR	NR	0	NR
Stomatitis/mucositis	1 (2)	NR	3 (9)	0	NR	NR	1 (2)	3 (10)
Hand–foot syndrome	1 (2)	NR	14 (44)	3 (10)	NR	NR	4 (7)	7 (23)
Proteinuria	6 (10)	NR	NR	NR	NR	NR	NR	NR
Asthenia	NR	NR	NR	NR	NR	NR	NR	NR
Dyspnoea	0	NR	NR	NR	NR	NR	0	NR
Dysphagia	NR	NR	0	NR	NR	NR	NR	NR
Rash	0	NR	Dermatology (other): 2 (6)	3 (10)	NR	NR	2 (4)	5 (16)

continued

TABLE 64 Incidence of grade ≥ 3 AEs reported from observational studies (*continued*)

	Observational study, *n* (%)							
Parameter	**Study 201**	**Study 208**	**Study 12636**	**UPCC-03305**[a]	**Chen *et al.***	**Duntas *et al.***	**Kloos *et al.*[a]**	**Study 12791**
Other types of grade ≥ 3 AEs	Other grade ≥ 3 AEs in ≥ 5% of patients: • Dehydration, 5 (9) • Arthralgia, 3 (5)	NR	Other grade ≥ 3 AEs reported: • Infection, 3 (9) • Arthralgia, 3 (9) • Drug hypersensitivity, 3 (9) • Constipation, 1 (3) • Muscle cramps, 1 (3) • Anaemia, 1 (3) • Fever, 1 (3)	• Elevated liver function tests, 2 (7) • Pruritus, 1 (3) • Sleep disturbance/anxiety, 1 (3) Terry *et al.* 2013[137] later examined hand–foot syndrome and rash. AE data for all 55 patients not RR-DTC only ($n = 47$) (treatment-related): • Hand–foot syndrome, 4 (7) • Rash, 9 (18)	'Although the types of toxicities were consistent with other sorafenib trials, their severity was relatively mild'[78]	NR	Grade ≥ 3 AEs reported, in text Most common (≥ 5% frequency) grade 3 AEs included: • Hand or foot pain (12) • Arthralgia (11) • Fatigue (16) • Hand–foot syndrome (7) • Musculoskeletal chest pain (7) • Asymptomatic hyponatraemia (5)	Grade 3 AEs: • Congestive heart disease, 1 • Deep vein thrombosis, 1 Grade 4 AEs: • Myocardial infarction, 3 (10) • Small cell lung cancer, 1 (3)

ATC, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma; NR, not reported.
a Treatment-related.

TABLE 65 Incidence of SAEs and fatal AEs reported from observational studies

	Observational study, *n* (%)							
Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen *et al.*	Duntas *et al.*	Kloos *et al.*	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
SAEs	28 (48)	NR	NR	NR	NR	NR	NR	NR
Types of SAEs	SAEs that occurred in at least two patients: • Dehydration (7) • Hypotension (5) • Pulmonary • embolism (3) • Lower abdominal pain (3) • Hypertension (3) • Cardiac failure (3)	NR	NR	NR	NR	NR	NR	NR
Fatal AEs	Deaths attributable to AEs, 3 (5%): • Progressive disease • Arterial haemorrhage • Cardiac arrest	Four deaths, all unrelated to study drug	NR	NR	NR	NR	1 (not considered treatment related)	NR

ATC, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma; NR, not reported.

TABLE 66 Dose modifications resulting from AEs reported in the prospective observational studies

Event	Prospective observational study		
	Lenvatinib, two studies,[77,135] treatment emergent (%)	Sorafenib, four studies,[59,78,81,126] treatment emergent (%)	Sorafenib, two studies,[88,101] treatment related (%)
AE dose interruptions	74[a]	82[a]	NR
AE dose reductions	66[a]	42 to 100[a]	47 to 52[b]/47 to 55[b,c]
AE discontinued	2 to 26[b]	23[a]	20[a]
Other	AEs that led to lenvatinib withdrawal and occurred in ≥ 3.5% patients in Study 201: • Proteinuria, 5 • Pulmonary embolism, 3 • Deep-vein thrombosis, 3	Two out of three patients with a PR withdrew from the study after 5–7 months of treatment in one study 79% of patients required a dose reduction by one dose level to 400 mg daily and one-third of these patients underwent a further reduction to the lowest dose level of 400 mg on alternate days in one study	

NR, not reported; PR, partial response.
a Incidence of AEs reported by one study.
b Range of AE incidence reported by two studies.
c Terry *et al.*[137] later examined treatment-related hand–foot syndrome and rash for UPCC-03305 (12192)[88] and data in the table are reported as ranges using earlier and later data cut-off points, respectively.

TABLE 67 Dose modifications reported from observational studies

	Observational study, *n* (%)							
Parameter	Study 201	Study 208	Study 12636	UPCC-03305[a]	Chen *et al.*	Duntas *et al.*	Kloos *et al.*[a]	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
AE dose interruptions	43 (74)	NR	28 (82)	NR	NR	NR	NR	NR
AE dose reductions	38 (66)	NR	NR	14 (47)	0	11 (100)	29 (52)	3 months: 13 (42) 6 months: 15 (52) 12 months: 18 (58)
AE discontinued	15 (26)	1	NR	6 (20)	NR	NR	NR	7 (23)
Other	AEs that led to lenvatinib withdrawal and occurred in at least two patients were: • Proteinuria (5) • Pulmonary embolism (3) • Deep-vein thrombosis (3)		79% of patients required a dose reduction by one dose level to 400 mg daily and one-third of these patients underwent a further reduction to the lowest dose level of 400 mg on alternate days	Terry *et al.* 2013[137] later reported 30 (55) dose reductions ($n = 55$)		2/3 with a PR withdrew from the study after 5 to 7 months of treatment		

ATC, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma; NR, not reported; PR, partial response.
a Treatment related.

TABLE 68 Other AE information reported from observational studies

	Observational study, *n* (%)							
Parameter	**Study 201**	**Study 208**	**Study 12636**	**UPCC-03305**	**Chen *et al.***	**Duntas *et al.***	**Kloos *et al.***	**Study 12791**
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC: 25	All: 34 RR-DTC: 19	All: 55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
Laboratory AEs	Clinically important changes in mean vital signs from baseline to the end points at various visits were observed. Blood pressure changes occurred and were reported as AEs if deemed clinically important by the investigator. Lenvatinib treatment was correlated with an increase in blood pressure		Liver abnormalities were common (32% of patients experiencing a grade 1/2 transaminitis; 15% of patients developed grade 3 amylasaemia) but no patients developed acute pancreatitis Lipase levels were found to be raised in 22% of patients, half of which were grade ≥ 3 12% of patients developed an elevated TSH. As all patients were on thyroxine (T4) replacement therapy and asymptomatic, this was interpreted as subclinical hypothyroidism corrected by increasing the T4 dose		There was a marked and rapid change in the serum thyroglobulin level after start of treatment, with a mean decrease of 60% within 12 weeks, consistent with radiographic findings	Tg level was variably decreased by up to 85%	Although dramatic sustained decreases in serum Tg levels were observed in some patients with PRs and stable disease, neither baseline Tg nor Tg response consistently correlated with degree or duration of objective response	Tg response reflected the radiological response; patients with a PR had a median decrease in their serum Tg levels. Patients with stable or progressive disease showed an increase in their serum Tg levels
Timing of AEs	Most of the increases in blood pressure were observed in the first cycle. Downwards trends in both systolic and diastolic blood pressure were observed after an increase, mainly owing to treatment with antihypertensive medications and/or dose interruption or reduction[316]			From Terry *et al.* 2013[137] (*n* = 55): The severity of skin toxicity peaked by cycle 1 for rash and cycle 2 for HFSR. The severity improved dramatically for rash by cycle 3 and for HFSR by cycle 6. Our data support the close supervision of skin-related AEs in the first six cycles of treatment with sorafenib. However, the sustained high prevalence of rash and HFSR requires that all patients receive ongoing skin care for the duration of therapy				*The majority of AEs were seen in the first year of treatment and were controllable with dose reduction, medication, or supporting measures (i.e. dietary consultation and additional feeding)*[126]

	Observational study, *n* (%)							
Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen *et al.*	Duntas *et al.*	Kloos *et al.*	Study 12791
Other	The authors[316] concluded that lenvatinib had an acceptable safety profile for patients with refractory thyroid cancer and no new safety concerns were observed	The authors[207] state: *Toxicities were manageable with dose modifications*	The authors[59] state: *This study demonstrates that sorafenib is tolerable at reduced doses over prolonged periods of time in patients with thyroid cancer. Sorafenib leads to radiological and biochemical stabilisation of disease in the majority of these patients despite dose reductions*	The authors[137] state: *Our data support the close supervision of skin-related AEs in the first six cycles of treatment with sorafenib. However, the sustained high prevalence of rash and hand-foot syndrome requires that all patients receive ongoing skin care for the duration of therapy*	The authors[78] state: *Prospective controlled randomised studies with more patients and longer observation times are greatly needed*	The authors[81] state: *However, the aggressiveness of disease in some patients implies that targeted therapy should take into account biomarkers and consider combinations with other TKIs or with mTOR inhibitors, adapting the dose, to enhance tolerability and response*	The authors[101] state: *Sorafenib is a reasonably well-tolerated therapy with clinical and biologic antitumour activity in metastatic PTC*	The authors[126] concluded: *Toxicity was consistent with other sorafenib trials*

ATC, anaplastic thyroid carcinoma; HFSR, hand–foot skin reaction; MTC, medullary thyroid carcinoma; mTOR, mammalian target of rapamycin; NR, not reported; PR, partial response; Tg, thyroglobulin.

Appendix 9 Ongoing studies (summary)

TABLE 69 Characteristics of the ongoing studies

	Study			
Parameter	**E7080–G000–21 (Study 211)**	**E7080–C086–308 (Study 308)**	**MATiSSe**	**NEXAVAR-TC-01 (Study 17391)**
Description	Postmarketing safety study of lenvatinib (Study 211)	Lenvatinib for RR-DTC in China	A pilot study evaluating the safety and efficacy of sorafenib	Postmarketing safety study of sorafenib
Sponsor	Eisai Ltd	Eisai Ltd	Royal Marsden NHS Foundation Trust	Bayer HealthCare
Commencement date	28 March 2016	7 February 2017	Ethics approval, 8 January 2007	27 June 2014
Expected end date	30 October 2020	April 2020	NR	30 June 2021
Participants	161 patients with RR-DTC	150 patients with RR-DTC	33 patients with RR-DTC or MTC	443 patients with RR-DTC
Outcomes	• ORR at 6 months • Percentage of treatment-emergent grade ≥ 3 AEs (up to 6 months) • PFS (up to 18 months) • PFS after next line of treatment (PFS2, up to 18 months after initiating next line of treatment) • Number of participants with treatment-emergent AEs and SAEs (up to 1 month) • Time to treatment discontinuation attributable to an AE (up to 1 month) • Dose reductions and interruptions (up to 1 month) • AUC of lenvatinib (predose and 2-hour to 12-hour postdose) • HRQoL (up to 18 months)	• PFS (up to 12 months) • ORR (up to 36 months) • OS (up to 36 months) • Number of participants with treatment-emergent AEs (up to 36 months)	• Proportion of patients who have achieved a response during 6 months of treatment with sorafenib • Proportion of patients achieving a response during 9 and 12 months of treatment with sorafenib • Biomarkers toxicity outcomes at 1, 3, 6, 9 and 12 months • PFS and OS	• Number of participants with adverse drug reactions (up to 9 months) • Number of participants with SAEs (up to 9 months) • Number of participants with serious adverse drug reactions (up to 9 months) • 2-year survival • Time to treatment failure (up to 9 months)

AUC, area under the concentration-time curve; MTC, medullary thyroid carcinoma; NR, not reported.

Appendix 10 Additional tables summarising key features of the companies' economic models

TABLE 70 Total monthly routine care costs

Parameter	Model costs (£)	
	Eisai Ltd	Bayer HealthCare
Pre-progression		
Response	280.61	–
Stable disease	297.98	–
Sorafenib and lenvatinib	–	Commercial in confidence
Placebo/BSC	–	Commercial in confidence
Progressive disease/post progression	1315.56	Commercial in confidence

Note
Information drawn from Eisai Ltd[8] (table 25) and Bayer HealthCare[7] (table 28).

TABLE 71 Adverse event frequencies/rates and costs

	Model							
	Eisai Ltd (lenvatinib)			Bayer HealthCare (sorafenib)				
	Frequency of grade 3 to 4 AE hospitalisations (%)			Rate of grade 3 and 4 AEs (per 28 days) (%)			Cost per patient per 28 days (£)	
Parameter	Lenvatinib	Sorafenib	Hospitalisation costs (£)	Lenvatinib	Sorafenib	Placebo/BSC	Grade 3	Grade 4
Hypertension	3.5	0.79	850.67	3.55	0.76	0.43	158	65.06
Weight decrease	0.40	0.19	639.83	0.67	0.58	0.19	345	–
Diarrhoea	0.40	0.28	571.30	0.55	0.55	0.13	223	102
Decreased appetite	0.40	0.00	639.83	–	–	–	–	–
Hypocalcaemia	0.40	0.69	615.83	0.18	0.72	0.30	9	9
Hypokalaemia	0.00	0.00	615.83	–	–	–	–	–
Asthenia	0.00	0.00	658.83	–	–	–	–	–
Fatigue	0.00	0.00	658.83	0.64	0.48	0.18	61	74
Hand–foot syndrome	0.00	1.40	450.35	0.23	1.64	–	155	–
Proteinuria	0.40	0.19	778.67	–	–	–	–	–

Note
Information drawn from Eisai Ltd[8] (tables 27 and 28) and Bayer HealthCare[7] (tables 23 and 30).

Appendix 11 The NICE reference case checklist (summary)

TABLE 72 The NICE reference case checklist: summary of the publications that were included in the AG's review of economic evidence

Attribute	Reference case	Erdal *et al.* 2015[163]	Huang *et al.* 2016[158,159]	Tremblay *et al.* 2016[160]	Wilson *et al.* 2017[161]	SMC 2015[48]	SMC 2016[38]	CADTH 2015[5]	CADTH 2016[162]
Decision problem	The scope developed by NICE	✓	✓	✓	✓	✓	✓	✓	✓
Comparator(s)	As listed in the scope developed by NICE	✓/✗	✓	✓	✓	✓/✗	✓	✓/✗	✓/✗
Perspective costs	NHS and PSS	✗	✗	✗	✗	✗	✗	✗	✗
Perspective benefits	All direct health effects, whether for patients or carers	✓/✗	✓/✗	✓	✓	✓	✓	✓	✓
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	✓	✓	✓	✓	✓	✓	✓	✓
Time horizon	Long enough to reflect all important differences in costs or outcomes	✓	✓	✓	✓	✓	✓	✓	✓
Synthesis of evidence on outcomes	Based on systematic review	✓	✓	✓	✓	✓	✓	✓	✓
Outcome measure	Health effects should be expressed in QALYs (EQ-5D preferred)	✓	NR	✓	✓	✓	✓	✓	✓
Health states for QALY	Reported directly by patients and/or carers	✓	NR	✓	✗	✓	✗	✗	✗
Benefit valuation	Time trade-off or standard gamble	✓	NR	✗	✓	✓	✓	✓	✓
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	NR	NR	✓	✗	NR	✗	NR	✗
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	NR	✗	✓	✓	NR	NR	NR	NR

✗, no (item not properly addressed); ✓, yes (item properly addressed); ✓/✗, partially (item partially addressed); NR, not reported; PSS, Personal Social Services.

Appendix 12 The Drummond checklist (summary)

TABLE 73 Drummond checklist summary of publications that were included in the AG's review of economic evidence

Question	Publication							
	Erdal *et al.* 2015[163]	Huang *et al.* 2016[158,159]	Tremblay *et al.* 2016[160]	Wilson *et al.* 2017[161]	SMC 2015[48]	SMC 2016[38]	CADTH 2015[5]	CADTH 2016[162]
Was a well-defined question posed in answerable form?	✓	✓	✓	✓	✓	✓	✓	✓
Was a comprehensive description of the competing alternatives given?	✓	✓	✓	✓	✓	✓	✓	✓
Was the effectiveness of the programme or services established?	✓	✓	✓	✓	✓	✓	✓	✓
Were all the important and relevant costs and consequences for each alternative identified?	✓	Unclear	✓	✓	✓	✓	Unclear	✓
Were costs and consequences measured accurately in appropriate physical units?	Unclear	Unclear	✓	✓	Unclear	✓	Unclear	✓
Were the cost and consequences valued credibly?	Unclear	Unclear	✓	✓/✗	Unclear	✓	Unclear	✓/✗
Were costs and consequences adjusted for differential timing?	Unclear	✓	✓	✓	Unclear	Unclear	Unclear	Unclear
Was an incremental analysis of costs and consequences of alternatives performed?	✓	✓	✓	✓	✓	✓	✓	✓
Was allowance made for uncertainty in the estimates of costs and consequences?	✓	✓	✓	✓	✓	✓	✓	✓
Did the presentation and discussion of study results include all issues of concern to users?	✓	✓	✓	✓	✓	✓	✓	✓

✗, no (item not properly addressed); ✓, yes (item properly addressed); ✓/✗, partially (item partially addressed).

Appendix 13 The NICE reference case checklists in full

TABLE 74 The NICE reference case checklist completed by the AG: Erdal *et al.* 2015

Attribute	Reference case	Does the economic evaluation match the reference case? (Erdal *et al.* 2015[163])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – sorafenib is compared with BSC but not to lenvatinib
Perspective: costs	NHS and PSS	Turkish payer's perspective taken
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Partial – patient related direct health effects were considered
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – lifetime horizon
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily taken from DECISION
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs and based on EQ-5D data collected in DECISION
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in DECISION
Benefit valuation	Time trade-off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Does not state in abstract which valuation set is used for the EQ-5D estimates of utility
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Sensitivity analysis was conducted, but no details of the methods used were reported

PSS, Personal Social Services.

TABLE 75 The NICE reference case checklist completed by the AG: Huang *et al.* 2016

Attribute	Reference case	Does the economic evaluation match the reference case? (Huang *et al.* 2016[158,159])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes – lenvatinib vs. sorafenib and both drugs vs. placebo. The placebo evidence is derived from the Phase III trials; the AG assumes placebo and BSC are equivalent comparators
Perspective: costs	NHS and PSS	US perspective. The authors states that direct medical costs were used, but some costs were sourced from Medicare Fee Schedule, which reflects tariffs rather than direct costs
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Partial – patient-related direct health effects were considered, although source and values were not reported in the abstract
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – lifetime horizon
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from DECISION and SELECT
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Authors state the utility values were taken from published sources, but it is unclear which measurement tools were used as the published sources were not referenced
Health states for QALY	Reported directly by patients and/or carers	Unclear
Benefit valuation	Time trade-off or standard gamble	Unclear
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Unclear but unlikely to be representative of UK population as the study is set in the USA
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes – 3% used
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Sensitivity analysis was conducted, but no details of the methods used were reported

PSS, Personal Social Services.

TABLE 76 The NICE reference case checklist completed by the AG: Tremblay *et al.* 2016

Attribute	Reference case	Does the economic evaluation match the reference case? (Tremblay *et al.* 2016[160])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes – lenvatinib vs. sorafenib
Perspective: costs	NHS and PSS	US perspective
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 5-year and 10-year results reported
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from DECISION and SELECT
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	QALYs – not EQ-5D
Health states for QALY	Reported directly by patients and/or carers	UK general population
Benefit valuation	Time trade-off or standard gamble	Neither
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes – 5% (details provided by lead author)
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Sensitivity analysis was conducted, but no details of the methods used were reported

PSS, Personal Social Services.

TABLE 77 The NICE reference case checklist completed by the AG: Wilson 2017

Attribute	Reference case	Does the economic evaluation match the reference case? (Wilson 2017[161])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective: costs	NHS and PSS	US health-care perspective
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – lifetime
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from SELECT and DECISION
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	No – utility is estimated from a vignette study generated from a sample of the general UK population in which participants were asked to value health-state scenarios they were presented with
Benefit valuation	Time trade-off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes – 3%
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Yes

PSS, Personal Social Services.

TABLE 78 The NICE reference case checklist completed by the AG: SMC 2015

Attribute	Reference case	Does the economic evaluation match the reference case? (SMC 2015[48])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – sorafenib is compared with BSC but not with lenvatinib
Perspective: costs	NHS and PSS	NHS Scotland
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – time horizon up to 10 years
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily taken from DECISION
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs and taken from EQ-5D data collected in DECISION
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in DECISION
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Does not state which valuation set is used for the EQ-5D estimates of utility
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis conducted, but no mention of PSA

PSS, Personal Social Services.

TABLE 79 The NICE reference case checklist completed by the AG: SMC 2016

Attribute	Reference case	Does the de novo economic evaluation match the reference case? (SMC 2016[38])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective: costs	NHS and PSS	NHS Scotland
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – time horizon up to lifetime
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from DECISION and SELECT
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	No – utility is estimated from a vignette study generated from a sample of the general UK population in which participants were asked to value health-state scenarios they were presented with
Benefit valuation	Time trade-off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Not applicable
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis was conducted, but there was no mention of PSA in the publication

PSS, Personal Social Services.

TABLE 80 The NICE reference case checklist completed by the AG: CADTH 2015

Attribute	Reference case	Does the economic evaluation match the reference case? (CADTH 2015[5])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – sorafenib is compared with BSC but not with lenvatinib
Perspective: costs	NHS and PSS	Canadian health-care perspective
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – up to 10 years
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from DECISION
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs and based on the EQ-5D data collected in DECISION
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in DECISION
Benefit valuation	Time trade-off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Does not state in the abstract which valuation set is used for the EQ-5D estimates of utility
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis was conducted, but there is no mention of PSA in the publication

PSS, Personal Social Services.

TABLE 81 The NICE reference case checklist completed by the AG: CADTH 2016

Attribute	Reference case	Does the de novo economic evaluation match the reference case? (CADTH 2016[162])
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – lenvatinib is compared with BSC but not with sorafenib
Perspective: costs	NHS and PSS	Canadian health-care perspective
Perspective: benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – up to 10 years
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from SELECT
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	No – utility is estimated from a vignette study generated from a sample of the general UK population in which participants were asked to value health-state scenarios they were presented with
Benefit valuation	Time trade-off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis was conducted, but there is no mention of PSA in the publication

PSS, Personal Social Services.

Appendix 14 Drummond checklists in full

TABLE 82 Critical appraisal checklist for the economic analysis completed by the AG: Erdal *et al.* 2015

Erdal *et al.* 2015:[163] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from DECISION
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Resource use estimates generated from an expert panel
Were costs and consequences measured accurately in appropriate physical units?	Unclear	Sources of cost evidence described, but no details of what was measured were reported
Were the cost and consequences valued credibly?	Unclear	Not reported
Were costs and consequences adjusted for differential timing?	Unclear	Not reported
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were calculated accurately
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	One-way and probabilistic sensitivity analysis were undertaken, but details of the methods and parameters varied were not reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

TABLE 83 Critical appraisal checklist for the economic analysis completed by the AG: Huang *et al.* 2016

Huang *et al.* 2016:[158,159] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from DECISION and SELECT
Were all the important and relevant costs and consequences for each alternative identified?	Unclear	Based on the Phase III trials, but does not report resource use or costs used within the model
Were costs and consequences measured accurately in appropriate physical units?	Unclear	Sources of cost evidence described, but no details of what was measured were reported
Were the cost and consequences valued credibly?	Unclear	Details of resource use estimates were not reported
Were costs and consequences adjusted for differential timing?	Yes	3% discount rate used
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	One-way and probabilistic sensitivity analyses were undertaken, but details of the methods and parameters that were varied were not reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

TABLE 84 Critical appraisal checklist for the economic analysis completed by the AG: Tremblay *et al.* 2016

Tremblay *et al.* 2016:[160] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from DECISION and SELECT
Were all the important and relevant costs and consequences for each alternative identified?	Partially unclear	Based on data from the Phase III trials, time trade-off utility values that were taken from the Kerr *et al.*[167] abstract (details provided via correspondence by lead author of paper). Details of resource use and costs were presented in the abstract. Details of discount rates were provided via correspondence with lead author (5%) [Dr Gabriel Tremblay, Purple Squirel Economics (previously at Eisai), June 2017]
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	% discount rate used for both costs and outcomes obtained through correspondence with lead author
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	PSA was mentioned in the conclusion, but no results or methods were reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

TABLE 85 Critical appraisal checklist for the economic analysis completed by the AG: Wilson 2017

Wilson 2017:[161] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from data collected in DECISION and SELECT
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partially	Utility estimates were from a published study rather than directly from the trial population
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost, QALYs, LYs and ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Parameter and probabilistic sensitivity analyses were conducted
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

LY, life-year.

TABLE 86 Critical appraisal checklist for the economic analysis completed by the AG: SMC 2015

SMC 2015:[48] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from DECISION
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Unclear	
Were the cost and consequences valued credibly?	Unclear	
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Results of multiple-parameter sensitivity analysis were reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

TABLE 87 Critical appraisal checklist for the economic analysis completed by the AG: SMC 2016

SMC 2016:[38] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from DECISION and SELECT
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Scenario and sensitivity analysis was completed
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

TABLE 88 Critical appraisal checklist for the economic analysis completed by the AG: CADTH 2015

CADTH 2015:[5] question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Not detailed in the report but effectiveness data were derived from DECISION
Were all the important and relevant costs and consequences for each alternative identified?	Unclear	Not reported
Were costs and consequences measured accurately in appropriate physical units?	Unclear	
Were the cost and consequences valued credibly?	Unclear	
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Results of several sensitivity analyses were presented
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

TABLE 89 Critical appraisal checklist for the economic analysis completed by the AG: CADTH 2016

CADTH 2016:[162] question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from data collected in DECISION and SELECT
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partially	From a published study[168] rather than directly from the trial population
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost, QALYs, LYs and ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Parameter sensitivity analysis was conducted
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ERG, Evidence Review Group; LY, life-year.

EME
HS&DR
HTA
PGfAR
PHR

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